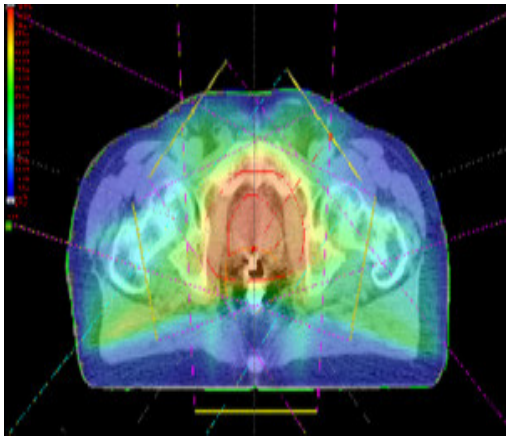
Sorveglianza Attiva nel carcinoma prostatico : CONS



Vittorio Vavassori
U.O. Radioterapia, Humanitas Gavazzeni
Bergamo

Sorveglianza Attiva : premessa

- Avvento di PSA e screening
- Stage migration verso “low risk”
- Incremento % pts con malattia clinicamente indolente/ insignificante a buona prognosi
- Incremento rischio sovra-diagnosi e sovra-trattamento / incremento morbidita’

in pts con malatia localizzata a basso rischio di progressione la Sorveglianza Attiva puo’ essere considerata trattamento appropriato

Sorveglianza Attiva : i postulati

- Lo screening identifica malattia priva di rilevanza clinica in una % non trascurabile di pts
- Possibilita' concreta di identificare questi pts
- I pts riclassificati ad alto rischio vengono ad ogni modo curati con trattamento radicale

- Vantaggi dall' astensione di trattamento attivo immediato (minor morbidita')

- Peso psicologico astensione < impatto su QoL di terapia immediata

Sorveglianza attiva : rischi vs benefici

Risks

- Anxiety caused by fear of progression, missing a window of opportunity and living with cancer
- Progression and mortality. Missing the window of opportunity for cure ultimately leads to poorer oncological outcomes and the need for adjuvant treatment
- Erectile dysfunction secondary to multiple biopsies or caused by anxiety

Benefits

- Reduced morbidity and improved quality of life compared to radical treatments. Avoidance of overtreatment, making early detection efforts for high-risk disease more appealing
- Less anxiety because the tumor does not require treatment and is therefore not life threatening
- Low costs. More resources can be focused on life-threatening cancers, thus reducing the burden of prostate cancer on health care systems

Klotz L., 2011

Sorveglianza Attiva : risultati

Outcomes of active surveillance in large prospective series

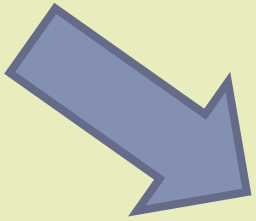
Study	*n*	Median follow-up (months)	Treated (%)	Disease-specific survival (%)	Biochemical recurrence after deferred treatment (%)
University of Toronto, Canada (2009)[39]	450	80	30 at 5 years	97 at 10 years	50 (13 overall)
Multicenter European study (2009)[17]	616	47	32 at 10 years	100 at 10 years	20*
University of California, San Francisco, USA (2008)[38]	328	43	24 at 5 years	100 at 5 years	NR
Multicenter Japanese study (2008)[67]	118	36	51 at 3 years	NR	NR
Johns Hopkins, USA (2007)[13]	407	NR	36 at 37 months	NR	NR (50% deemed 'incurable' based on postsurgery pathology)
Rotterdam, The Netherlands (2007)[68]	273	41	29 at 5 years	100 at 5 years	NR (31% of prostatectomy specimens had positive margins)
University of Miami, USA (2010)[5]	230	32	14 at 3.7 years	100 at 2.7 years	0
Royal Marsden, UK (2005)[69]	80	42	14 at 5 years	NR	0
Memorial Sloan Kettering, USA (2004)[70]	88	35	35 at 5 years	NR	NR

*12% received adjuvant hormone therapy, so true recurrence rate unknown. Abbreviation: NR, not reported.

Lawrentshuck N e Klotz L , 2011

Sorveglianza Attiva : risultati-commento

- Circa 1/3 pts riclassificato e trattato
- Nei pts trattati 32-50% di recidiva biochimica
- Nessuna differenza in mortalita' o % metastasi
- Nell'ambito di 5 yrs mortalita' molto bassa
- Il rischio di morte per altre cause e' > rischio di morte per cancro della prostata



assenza di studi comparativi;
studi di coorte, risk mixed,y/n screened ;
disomogenei criteri inclusivi e strategie osservazionali differenti ;
eta',comorbidita',aspettativa di vita??
offerta, accettazione e aderenza al protocollo?

Ann Intern Med. 2012;156:582-590.

REVIEW | Annals of Internal Medicine

Active Surveillance in Men With Localized Prostate Cancer

A Systematic Review

Issa J. Dahabreh, MD, MS; Mei Chung, PhD, MPH; Ethan M. Balk, MD, MPH; Winifred W. Yu, PhD, MS; Paul Mathew, MD; Joseph Lau, MD; and Stanley Ip, MD

Conclusion

Since the introduction of PSA screening, more men have been diagnosed with early-stage, low-risk prostate cancer. The comparative effectiveness of AS versus immediate active treatment remains unclear. A standard, universally accepted use of the term AS that clearly distinguishes it from WW and other observational management strategies is needed to promote scientific discourse in this field. Future clinical studies are needed to determine the optimal AS protocol and provide information on the comparative effectiveness of AS versus immediate active treatment. These studies will require large sample sizes and long-term follow-up.

Sorveglianza Attiva
Criteri di selezione,monitoraggio, soglie di intervento

Selection criteria and triggers for intervention in active surveillance protocols

Variable	Active surveillance protocol					
	University of Toronto, Canada[39]	Johns Hopkins, USA[13,66]	Multicenter European study (PRIAS)[17]	University of California, San Francisco, USA[38]	University of Miami, USA[5]	Multicenter Japanese study[67]
Clinical stage	T1c	T1c	T1c or T2	T1 or T2a	NI	T1c
PSA (ng/ml)	≤10–15	NI	≤10	≤10	NI	≤20
Gleason score on biopsy	≤3+3=6*	≤3+3=6	≤3+3=6	≤3+3=6	NI	≤3+3=6
PSA density (ng/ml per ml)	NI	≤0.15	<0.2	NI	NI	NI
Number of positive cores on biopsy	NI	2‡ (core total not specified)	2 (of 8–12 cores)	<33% biopsy cores‡	≤2§ (of 10 cores minimum)	2‡ (of 6–12 cores)
PSA and DRE monitoring	3 monthly PSA and 6 monthly DRE for 2 years; 6 monthly PSA and annual DRE thereafter	6 monthly PSA and DRE	3 monthly PSA and 6 monthly DRE	3 monthly PSA with TRUS at 6–12 month intervals	3–4 monthly PSA and DRE for 2 years; 6 monthly thereafter	2 monthly PSA for 6 months; 3 monthly thereafter. DRE with TRUS at least every 6 months
Re-biopsy	6–12 months in the first year then every 2–3 years	Annually	At 1, 2 and 7 years or cT3 or PSADT ≤3 years (changed to ≤10 years in recent years)	Every 1–2 years	Annually or triggered by PSA or DRE change	At 1 year
Trigger for curative intervention	PSADT <3 years	Surveillance biopsy breaching selection criteria; patient request	Gleason score ≥7; >2 positive cores on biopsy	Gleason upgrade; increase in PSA velocity of 0.75ng/ml per year	Gleason upgrade; increase in tumor volume; >2 positive cores on biopsy	PSADT ≤2 years; pathological change breaching selection criteria

*Gleason score 7 in men over 70 years old. ‡<50% of cancer in any core. §≤20% of cancer in any core. Abbreviations: DRE, digital rectal exam; NI, not included; PSADT, prostate-specific antigen doubling time; TRUS, transrectal ultrasonography.

Lawrentschuk N e Klotz L., 2011

Sorveglianza Attiva : criticita'

- Criteri di selezione pts
- Strumenti di valutazione/predizione del rischio
- Monitoraggio del rischio di progressione
  - biopsia, PSA e derivati, imaging
- Accuratezza degli indici di progressione
- Soglie di intervento

- Effetto sulla terapia differita ?

Sorveglianza Attiva : si presume che…

- Il tumore diagnosticato e' insignificante o indolente e gli strumenti utilizzati sono adeguati
- La progressione eventuale del tumore puo' essere accuratamente monitorata
- Se il tumore progredisce, sara' curabile; il trattamento potrebbe non essere richiesto o significativamente dilazionato
- Morbidita' ed outcomes funzionali migliori
- Outcomes oncologici non differenti

Insignificant or indolent prostate cancer

Criteri (bps) di Epstein :

T1c, PSA density<0,15 ng/ml per gram, no GS= 4 or 5,

<3 bps + , <50% del core +

Predittivi per:.

- volume tumorale <0,2 cm3
- GS patologico <= 6
- malattia organo-confinata

Table II. Entry criteria for active surveillance (authors in alphabetic order).

Source	Entry criteria
Dall'Era et al. [1] (Most common clinical criteria)	Gleason score 6 No Gleason pattern 4 or 5 PSA level <10 ng/ml and stable PSA kinetics ≤50% single core involvement ≤33% positive cores
D'Amico et al. [5]	PSA level ≤10 ng/ml No Gleason pattern 4 or 5 Clinical stage T2a or lower
Epstein et al. [4]	Clinical stage T1c PSA density <0.15 ng/ml/cm^3 No Gleason pattern 4 or 5 <3 positive cores <50% cancer per core
Patel et al. [6]	Clinical stage T3 or lower Gleason sum ≤7
PRIAS* (Van den Bergh et al.) [9]	Clinical stage T1c–T2b No Gleason pattern 4 or 5 PSA density <0.20 ng/ml/cm^3 PSA level <10 ng/ml Fewer than three positive cores
Soloway et al. [7]	Clinical stage T2 or lower PSA level <15 ng/ml No Gleason pattern 4 or 5 <50% cancer per two positive cores
Van As et al. [8]	Clinical stage T1–T2a Gleason sum ≤7 (3 + 4) PSA level <15 ng/ml <50% of biopsy cores positive

*PRIAS, Prostate Cancer Research International Active Surveillance.

Selection criteria for active surveillance in PCa

Mufarrji PW, J Urol, 2009

- Retrospective study, N = 1,565 pts with localised PCa who underwent radical prostatectomy
- Outcomes in subgroups that fulfilled published criteria for active surveillance (Klotz-Toronto or Carter-Hopkins)

	Klotz* (N = 205)	Carter** (N = 71)
Upgrading to Gleason score ≥ 7	51.7%	51.0%
Primary Gleason score 4 or 5	13.7%	12.3%
pT3	7.8%	10.9%

* Klotz L. Urol Oncol 2006;24:46-50, ** Carter HB et al. J Urol 2007;178:2359-64

Candidates for active surveillance should be carefully selected and followed-up

Upgrading in pts fulfilling criteria for active surveillance (AS) who undergo surgery

Gomez-Veiga F. J Urol 2012;187(4 Suppl):e597-8(abs.1474)

- Single-centre retrospective study in pts who fulfilled criteria for AS but underwent RP (1999-2008)
  - N=212 fulfilling PRIAS criteria: PSA <10 ng/ml; PSADT≤2.2; cT1 or cT2; GS ≤6; ≤2 core positive Bx → **40.6% upgrading**
  - N=353 fulfilling START criteria: PSA <10 ng/ml; <cT3; GS ≤6 → **47.9% upgrading**
- Mean FU: 56 mo (range: 30-154)

	PRIAS				START			
	1 yr	2 yrs	5 yrs	10 yrs	1 yr	2 yrs	5 yrs	10 yrs
Progression-free survival (%)	94.2	86.1	75.2	53.8	92.6	85.5	68.0	52.7
Biochemical recurrence (%)	4.8	12.4	18.9	25.6	5.1	11.9	24.6	30.7
Death (%)	1.0	1.5	5.9	20.6	2.3	2.6	7.4	16.6

Selection of pts for AS has to be careful; new diagnostic tools to define aggressive tumours are needed

Frequency of upgrading, upstaging and significant tumour in pts eligible for active surveillance (AS)

El Hajj A. Eur Urol Suppl 2012;11(1):abs.757

- Retrospective analysis (2001-2011): N=1,161 pts who underwent RP for PCa
- Evaluation of pathological results in pts eligible for 6 international AS protocols

Type of AS protocol	N (%) pts eligible for AS	Upgrading (Gleason >6)	Upstaging (>T2)	Sign. tumour (>T2 and/or Gleason >6)	SVI (≥T3b)
Johns Hopkins	191 (16%)	45%	15%	46%	0%
PRIAS	306 (26%)	48%	18%	50%	0%
UCSF	395 (34%)	51%	20%	53%	0%
University of Toronto	485 (42%)	41%	24%	45%	4%
Royal Marsden	796 (69%)	38%	24%	42%	0%
MSKCC	830 (72%)	38%	24%	40%	0%

The AS protocol (Johns Hopkins) that is the most stringent for # pos. Bx cores (≤2) and % single core involvement (≤50%), has the lowest risk of upstaging

Insignificant or indolent prostate cancer

- Controverso data-set per criteri di selezione
- Variabilita' accuratezza predittiva dei criteri di selezione
- Quota non trascurabile di pts dimostra malattia non organo-confinata
- Accuratezza predittiva dei nomogrammi non ancora ottimale e dipendente dai criteri di selezione utilizzati e dalla popolazione studiata; necesita' di validazione esterna
- **Servono fattori clinici, biologici , (molecolari ?) per superare il paradigma low volume /low grade ed i termini :focale, malattia minima , tumore insignificante, very low risk ,etc**

Bastian PJ et al, Eur Urol, 2009
Bangma CH,Roobol MJ, Critical Rev Oncol/Hematol, 2012

Sorveglianza Attiva : biopsie

- Tecnica condiziona tumor detection
- Schemi espansi (12-21bps) > bps a sestante
- Rischio di undergrading :20-30% per 12 core bps
- Serialita' del campionamento per intercettare undersampling e de-differenziazione
- Suggerita biopsia confirmatoria per undersampling (21.5-35% pts ineleggibili)- MSKCC/PRIAS
- Rischio di grade progression:22-30%/ round -UCSF

Dall'Era MA et al , Eur Urol, 2012
Lees K et al, Curr Opin Urol, 2012

Sorveglianza Attiva : biopsie

- Controverso intervallo di tempo per bps
- Controverso n^ di cores (>-12/ zona anteriore ?)
- “Saturation” bps (zona di transizione, periferia)
  -30-50% upgrade/upstage;solo per restaging?-
- Il 30-40% pts va incontro a riclassificazione GS entro 2 yrs (misclassification!)
- Mapping + template transperineale (zona anteriore)
  -GS upgrading nel 27%/> tumor volume in 31%
  - 50 cores!

Wu JN et al, Scient World J, 2010
Dall’Era MA et al , Eur Urol, 2012
Lees K et al, Curr Opin Urol, 2012

Sorveglianza Attiva : soglie di intervento

- Gleason score >(=) 7
- PSAv > 0.75 o > 1 ng/ml/anno
- PSA-DT < 3 anni

- Cores coinvolti > 2
- Percentuale di cores con canro > 50%
- Incremento del volume (DRE, TRUS, bps)
- Giudizio clinico, decisione del paziente

Does one size fits all ?

Sorveglianza Attiva : soglie di intervento

- cinetica del PSA : risultati conflittuali sul ruolo predittivo per progressione; assenza di consenso su cut-off ottimale per guidare bps
- bps : incertezza sul cut-off appropriato per GS e size per definire quando intervenire

- Progressione vs riclassificazione
- Intensificazione sorveglianza vs intervento
- Giudizio clinico, decisione del paziente

One size doesn’t fit all !

Sorveglianza Attiva : focus on…

- Accuratezza diagnostica non elevata
- GS bioptico sottogradua % pts
- Il piccolo volume alla biopsia non e' in grado di predire il reale stato patologico (ECE+,SM+,N+)
- La cinetica del PSA e' strumento imperfetto per predire il rischio di evoluzione sfavorevole

- Ruolo di MRI imaging
- Necessita' di markers molecolari
- Ruolo e significato della terapia focale

Sorveglianza Attiva : morbidita’

- Ripetizione delle bps
  - > rischio di sepsi BPS correlato
  - > 2x rischio di ospedalizzazione
  - > rischio di disfunzione erettile
- > ansia in circa il 20-40%pts
- > LUTS

Fujita A et al, J Urol , 2009
Nam RK et al, J Urol, 2010
Glass L et al J Urol , 2012

Sorveglianza Attiva : si presume che…

- Il tumore diagnosticato e' insignificante o indolente e gli strumenti utilizzati sono adeguati (è elemento > criticita' !)
- La progressione eventuale del tumore puo' essere accuratamente monitorata (triggers + appropriati da definire)
- Se il tumore progredisce, sara' curabile / il trattamento potrebbe non essere richiesto o significativamente dilazionato (possibile upgrade e upstage /probabile)
- Morbidita' ed outcomes funzionali migliori (da dimostrare, ruolo del counselling fondamentale)
- Outcomes oncologici non differenti (dati preliminari incoraggianti, follow- up ancora breve / quali end points?)

Sorveglianza Attiva :pronta per il prime time?

- Overtreatment pts low risk probabile
- Sorveglianza Attiva da indagare; risultati incoraggianti ma da verificare nel lungo periodo
- Incertezze e criticita' nella metodologia
- Multidimensionalita' della problematica
- Si impone una reale e praticata multidisciplinarieta'
- Preferibile un percorso del pz in studi controllati

Probabilmente no; serve prudenza

Risk of recurrence after RP in pts eligible for active surveillance (AS) using PRIAS criteria

El Hajj A. Eur Urol Suppl 2012;11(1):abs.1090

- Retrospective analysis (1991-2010): N=626 pts who underwent RP for localised PCa and who met PRIAS criteria (T1c/T2, PSA ≤10 ng/ml, PSA density <0.2 ng/ml/cc, Gleason score <7, 1 or 2 pos. biopsies); median FU: 24 mo
- Pos. surgical margins (SMs): N=113 (18%)
- Biochemical recurrence = PSA >0.2 ng/ml

Tumour type	N	5-yr RFS	10-yr RFS	*P*
Significant tumour (>pT2 or Gleason score >6)	312	93.3%	85.6%	0.06
Non-significant tumour	312	87.6%	82.8%	

- **Regression analysis**: predictors for biochem. recurrence-free survival (RFS)

Potential predictor for RFS	Univariate analysis (*P*)	Multivariate analysis (*P*)
Pos. SMs	<0.001	<0.0001
Pathological stage	<0.0001	0.006
Gleason score	0.01	not significant

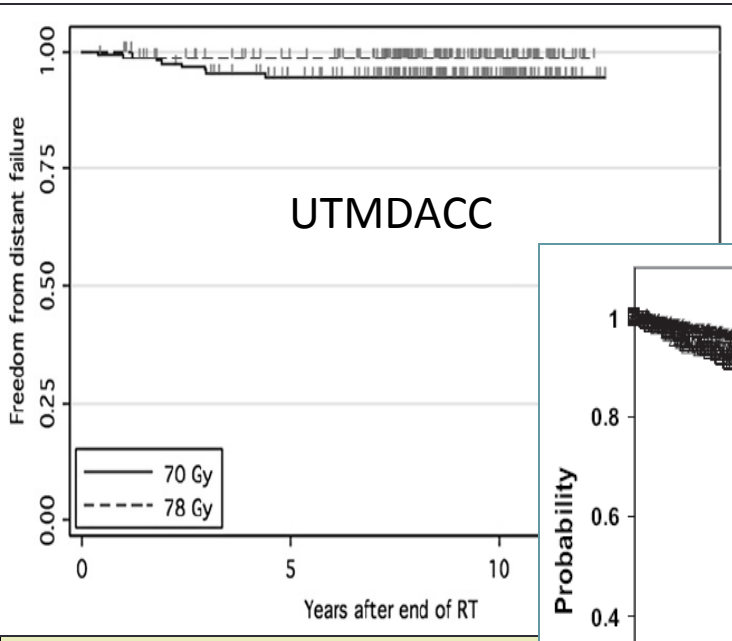
Pos. SMs, but not clinical significance of the tumour, seem to independently predict biochemical recurrence after RP in pts meeting the PRIAS criteria

Data from poster

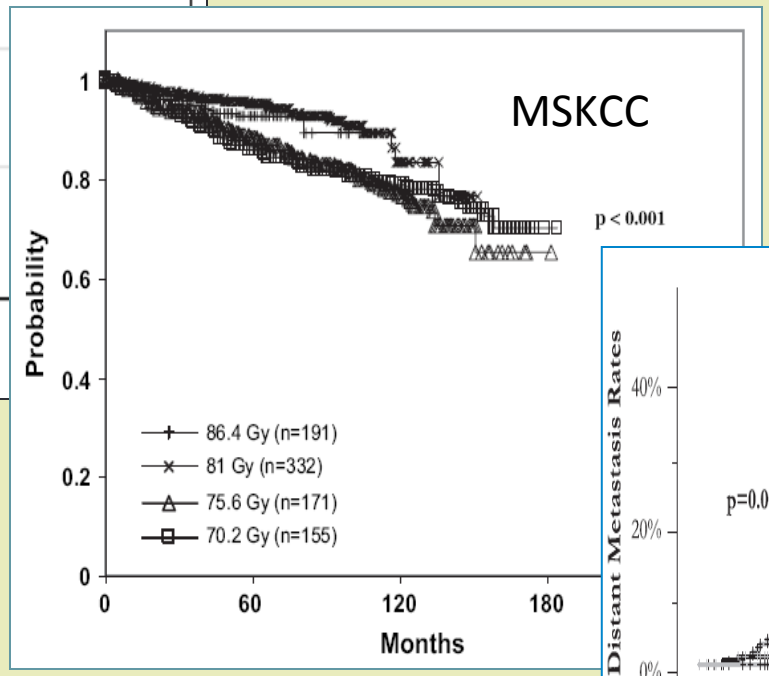
“Burden “: ruolo per evoluzione della malattia?

EBRT dose escalation
Freedom from Distant Metastases

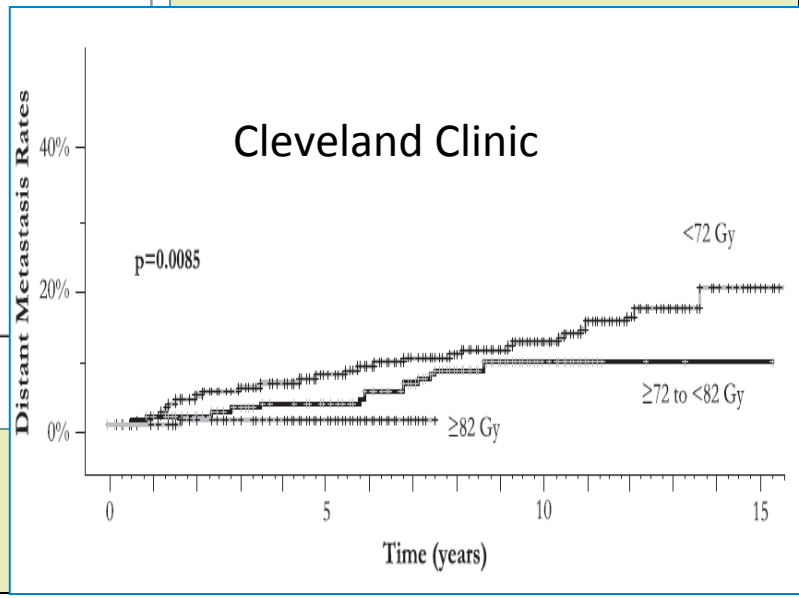
UTMDACC



MSKCC



Cleveland Clinic

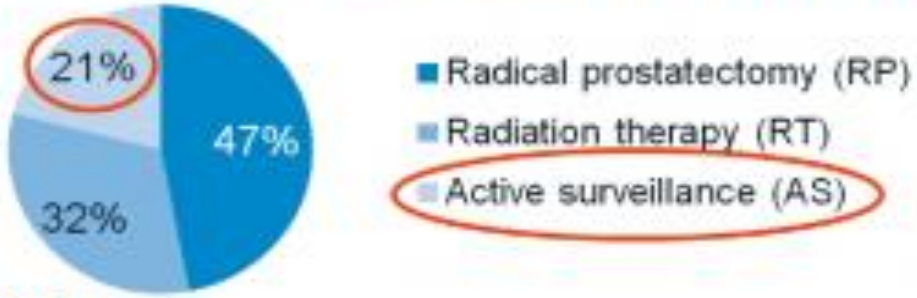


Physician's attitude towards active surveillance for low-risk PCa pts

Kim SP. J Clin Oncol 2012;30(15S):315s(abs.4657)

- Mail survey among urologists (N=322) and radiation oncologists (N=321) in the US (2011-2012)
- Low-risk PCa defined as: PSA <10 ng/ml, T1c, GS 6 in 1 core (12-core biopsy)

% of physicians recommending particular treatment for low-risk PCa



- **Multivariate analysis:**
  - Radiation oncologists more likely to recommend RT (OR=10.97; $P<0.001$)
  - Urologists more likely to recommend RP (OR=4.69; $P<0.001$) or AS (OR=2.18; $P=0.001$)

AS is recommended only to 21% of low-risk PCa pts in the US. This % is considerably lower than for RP or RT, although all 3 treatments are valuable options in these pts

Sorveglianza Attiva : principali studi

– Summarized key findings from the largest published series within the past 2 yr

Institution	Yr	Age, median	n	Follow-up, yr, median	No. treated (%)	Time to treatment, median	Primary trigger for treatment	Treated at 2 yr, %	PCSM, %	ACM, %
Johns Hopkins [8]	2011	66	769	2.7	255 (33)	2.2	Histology	19	0	2
University of Toronto* [9]	2010	70.3	450	6.8	135 (30)	NR	PSA	16	1	21.4
UCSF* [24]	2011	61.9	649	3.9	113 (30)**	3.5	Histology	-	0	3
ERSPC* [25]	2009	66	988	3.9	197 (32)	2.6	NR	22	0.2	11.2
Royal Marsden Hospital* [12]	2008	67	326	1.8	65 (20)	1.3	PSA	NR	0	2
MSKCC [13,26]	2011	62	238	1.8***	25 (11)	NR	Histology	NR	NR	NR
University of Miami [15,27]	2011	64	272	2.9	67 (25)	2.6	Histology	NR	0	2

PCSM = prostate cancer-specific mortality; ACM = all-cause mortality; NR = not recorded; PSA = prostate-specific antigen; UCSF = University of California, San Francisco; ERSPC = European Randomized Study of Screening for Prostate Cancer; MSKCC = Memorial Sloan-Kettering Cancer Center.

* Studies with some men having Gleason >3 + 3 disease.

** Percentage treated is of 337 men meeting strict inclusion criteria.

*** Median follow-up for patients without progression.

Dall'Era et al, Eur Urol, 2012