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Active surveillance for Gleason 3 + 4 prostate cancer: yes or no?

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Active surveillance for low-risk prostate cancer

- Strategy to delay or prevent active treatment (RP, EBRT) and its related side-effects (erectile dysfunction, incontinence)
- Men on AS have improved QoL outcomes compared to men who have received EBRT or RP
- Strict follow-up is indicated in men on AS with repeated biopsies according to a protocol

Eligibility criteria for AS according to most guidelines

Table 2 | Eligibility criteria

Guidelines	Risk category	PSA (ng/ml)	Positive cores (n)	Maximum extent cancer per core	Minimum cores sampled (n)
AUA[44]	Low		NR	NR	NR
	Intermediate		NR	NR	NR
	High		≤2	≤50%	10
EAU[45]	Low		≤2	≤50%	NR
NCCN[46]	Very low		<3	≥50%	NR
	Low		NR	NR	NR
NICE[48]	Low		NR	NR	NR
	Intermediate		NR	NR	NR
GSU[50]	Low		≤2	≥50%	10–12
DUA[49]	Low		1 or 2	NR	NR
	Intermediate		NR	NR	NR
	High		NR	NR	NR
KCE[51]	Low		NR	NR	NR
FCCG[54]	Low		<3	NR	10–12
	Intermediate		<3	NR	10–12
SCAN[52]	Low		<50% of biopsy cores affected	<50%	NR
CCNS[55]	Low		NR	NR	NR
	Intermediate		NR	NR	NR
I-CS[56]	Low		NR	<50%	>10
AHS[58]	Low		≤3	≤50%	10
CCO[59]	Low		NR	NR	NR
NCCS[61]	Low		<3	≥50%	NR
PCF[62] [REF. 22]	Very low		<3	<50%	NR
	Low		NR	NR	NR
PCFA[63]	NR		NR	NR	NR

Eligibility criteria:

- T-stage ≤T2
- PSA <10 ng/ml
- Gleason score ≤6
- Positive cores ≤2
- MCCI ≤50%

Bruinsma et al. Nat Rev Urol. 2016.

Active surveillance for low-risk prostate cancer is safe

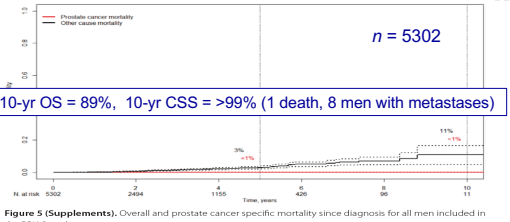
Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	n	Median FU (mo)	pT3 in RP patients	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [356]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [350]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [357]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [358]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [359]	278	41	-	89	100
Khatami, *et al.* 2007 [360]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [361]	993	77	-	85	98.1
Tosoian, *et al.* 2015 [355]	1,298	60	-	93	99.9
Total	**4,204-4,671**	**46.5**	-	**93**	**100**

10-yr CSS = 99 – 100% in men on AS

Active surveillance for low-risk prostate cancer is safe

PRIAS



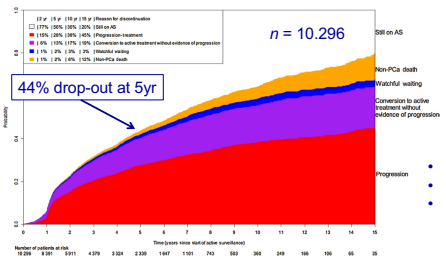
10-yr OS = 89%, 10-yr CSS = >99% (1 death, 8 men with metastases)

Figure 5 (Supplements). Overall and prostate cancer specific mortality since diagnosis for all men included in the PRIAS study.

Bokhorst et al. Eur Urol. 2016.

Many men reclassify at short-term follow-up

MOVEMBER Global Action Plan - 3



- GS 3+3 PCa
- 21 centers
- 12 countries

Fig. 1 – Cumulative incidence of discontinuation of active surveillance over time. AS = active

Van Hemelrijck et al. Eur Urol. 2019.

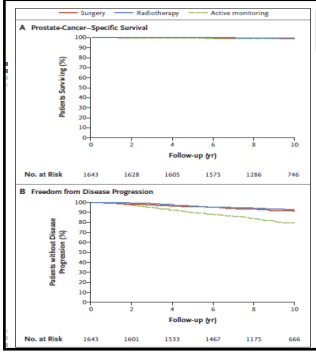
Why should we consider Gleason 3+4 PCa for AS?

- Many men do not meet the strict eligibility criteria
- Many men reclassify (GS upgrading) at short-term follow-up
- The majority of men with Gleason 3+4 PCa will not benefit from active treatment (competing risks / death by other causes)
- Improved tumor characterization by MRI-targeted biopsy might increase the safety of AS in Gleason 3+4 PCa

AS for Gleason 3+4 PCa within study cohorts

Table 2. Inclusion criteria for different active surveillance studies.

Active surveillance study	Criteria for inclusion
Royal Marsden[44]	Gleason <=3+4 (primary Gleason grade <=3); PSA <=15 ng/ml; cT1c-2a; <=50% of cores positive
University of Miami[45]	Gleason <=6; PSA <=15 ng/ml; cT1c-2c; <= two cores positive; <=20% of any core positive
Johns Hopkins[46]	Gleason <=3+3; PSA density <= 0,15 ng/ml/ml; cT1c; <= two cores positive; <=50% of any core positive
University of California San Francisco[47]	Gleason <=3+3; PSA <=10 ng/ml; cT1c-2c; <= 33% of cores positive; <=20% of any core positive
University of Toronto[48]	Gleason <=6; PSA <=10 ng/ml (until January 2000, for men age >70 years: Gleason <=3+4; PSA <= 15 ng/ml)
Prostate cancer Research International Active Surveillance (PRIAS)[49]	Gleason <=3+3; PSA <=10 ng/ml; PSAD <= 0,2 ng/ml/ml; cT1c-2c; <= two cores positive (age >70 years: Gleason <=3+4, maximum 10% tumor per cores)



ProtecT trial
Hamdy *et al.* NEJM. *2016.*

- 75% Low-risk PCa
- Randomization:
  AS (545) : RP (553) : EBRT (545)
- Similar 10-yr CSS
- Twice as many M+ in AS group

AS cohort with long-term follow-up (20% GS ≥3+4)

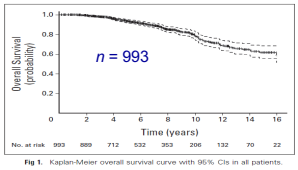


Fig 1. Kaplan-Meier overall survival curve with 95% CIs in all patients.

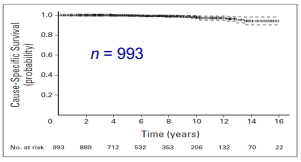


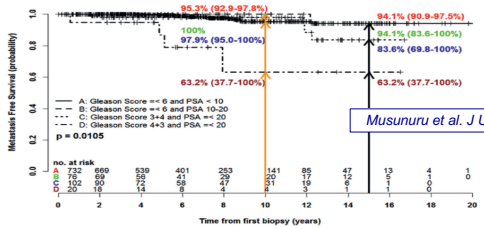
Fig 2. Kaplan-Meier cause-specific survival curve with 95% CIs in all patients.

10-yr OS = 80%, 15-yr OS = 62%

10-yr DSS = 98%, 15-yr CSS = 94%

Klotz et al. JCO. 2015.

AS for Gleason ≥3+4 PCa: high-risk of metastases



Musunuru et al. J Urol. 2016.

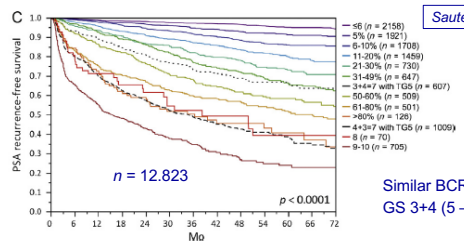
- GS 3+4 PCa: 16% of men with metastases after 15 years
- GS 4+3 PCa: 37% of men with metastases after 15 years

Is Gleason 3+4 PCa always unsuitable for AS?

Can we identify subgroups of men who might by suitable? based on:

- Extent or percentage of pattern 4 in biopsy
- Growth pattern (cribriform *vs* non-cribriform, intraductal carcinoma)
- Imaging (MRI)

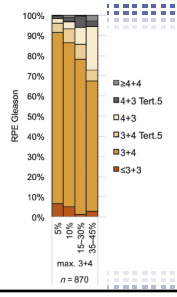
Strong correlation between %Gr4 and BCR after RP



Sauter et al. Eur Urol. 2016.

Similar BCR of GS 3+3 and GS 3+4 (5 – 10% Gr4) PCa

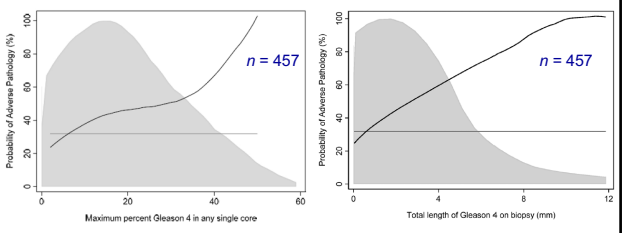
Strong correlation between %Gr4 and adverse pathology after RP



- Adverse pathology = GS ≥4+3, SVI, N+
- GS 3+4 PCa in 1 – 2 biopsy cores = 25% chance of adverse pathology
- GS 3+4 with 5 – 10% Gr4 has similar risk of adverse pathology compared to GS 3+3 PCa

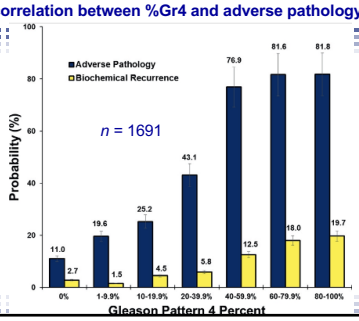
Sauter et al. Eur Urol. 2016.

Strong correlation between %Gr4 and adverse pathology after RP



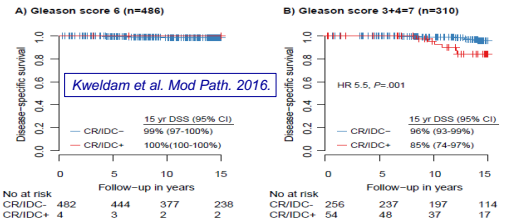
Dean et al. J UROL. 2019.

Strong correlation between %Gr4 and adverse pathology after RP



Cole et al. J UROL. 2016.

Strong correlation between cribriform / IDC and CSS



Kweldam et al. Mod Path. 2016.

- Similar CSS of GS 3+3 and GS 3+4 PCa without cribriform/IDC
- Significantly worse CSS in men with cribriform/IDC (*HR* = 5.5)

Molecular Hallmarks of Multiparametric Magnetic Resonance Imaging Visibility in Prostate Cancer

Kathleen E. Houlahan[a,b,c,†], Amirali Salmasi[d,†], Taylor Y. Sadun[d], Aydin Pooli[d], Ely R. Felker[e], Julie Livingstone[a], Vincent Huang[a], Steven S. Raman[e], Preeti Ahuja[e], Anthony E. Sisk Jr.[f], Paul C. Boutros[a,b,c,d,g,h,i,j,k,], Robert E. Reiter[d,l,k,m,*]*

- Case-control study (*n* = 40):
  - 20 patients with PI-RADS 2 (non-visible) MRI and Gleason 3+4 PCa at RP
  - 20 patients with PI-RADS 5 (visible) MRI and Gleason 3+4 PCa at RP
- Profiling of transcriptomic and copy number profile
- MRI-visible tumors seem to be more aggressive: genomes with increased mutation density, more cribriform/IDC, altered abundance of 102 transcripts

Houlahan et al. Eur Urol. 2019.

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Conclusions:

- Men with GS 3+4 PCa on AS have a higher risk of metastatic progression
- Therefore, men with GS 3+4 PCa should generally receive active treatment
- However, some men with favorable GS 3+4 PCa (≤10% gr4, no cribriform/IDC) might be eligible for AS
- Patient characteristics (age, comorbidities) and MRI should be considered when selecting men with favorable GS 3+4 PCa for AS

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THANK YOU
for your
ATTENTION!