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Using prognosis to guide inclusion criteria, define standardized end-points and stratify follow up in active surveillance for prostate cancer

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Abstract

Objectives

To test whether using disease prognosis can inform a rational approach to Active Surveillance (AS) for early prostate cancer

Methods

We previously developed the Cambridge Prognostics Groups (CPG), a 5-tiered model that uses PSA, Grade Group and stage to predict cancer survival outcomes. We applied the CPG model to a UK and a Swedish prostate cancer cohort to test differences in prostate cancer mortality (PCM) in men managed conservatively or by upfront treatment in CPG2 and 3 (which subdivides the intermediate-risk classification) versus CPG1 (low-risk). We then applied the CPG model to a contemporary UK AS cohort which was optimally characterised at baseline for disease burden to identify predictors of true prognostic progression. Results were retested in an external AS cohort from Spain.

Results

In a UK cohort (n=3659) 10-year PCM was 2.3% in CPG1, 1.5% & 3.5% in treated/untreated CPG2 and 1.9% & 8.6% in treated/untreated CPG3. In the Swedish cohort (n=27,942): 10-year PCM was 1.0% in CPG1, 2.2% & 2.7% in treated/untreated CPG2 and 6.1% & 12.5% in treated/untreated CPG3. We then tested using progression to CPG3 as a hard endpoint in a modern surveillance cohort (n=133). During follow-up (median 3.5 years) only 6% (8/133) progressed to CPG3. Predictors of progression were a PSA density ≥0.15 and CPG2 at diagnosis. Progression occurred in 1%, 8% and 21% of men with neither factor, only one or both. In an independent Spanish AS cohort (n=143) the corresponding rates were 3%, 10% and 14%.

Conclusion

Using disease prognosis allows a rational approach to inclusion criteria, discontinuation triggers and risk-stratified management in AS.

Background

Active surveillance (AS) is now the default management for men with low-risk prostate cancer and is becoming increasingly popular as an option for men with intermediate-risk disease [1-2]. Designing criteria for inclusion, optimal surveillance regimes and triggers for discontinuation however continues to be problematic because of a lack of level 1 trial evidence and there is great variability in urological practice [3-5]. The traditional endpoints for clinical trials such as survival and metastases are not easily applicable to AS cohorts because of the long natural history of the disease. This is clearly evident from recent large trials which, while not using contemporary AS strategies, have shown that the majority of men diagnosed with low/intermediate-risk disease and managed conservatively have very few adverse events even at 10 years [6]. As a result, there are no studies which have shown that any one surveillance protocol is any better than another nor is there

consensus on whether men with intermediate-risk disease should or should not be surveyed [7]. Key to attempting any such study is a clear idea of what the endpoint of AS should be i.e. when surveillance becomes unsafe and treatment becomes beneficial. While it is clear that the presence of high-risk features mandates treatment the critical question is whether a change from low-risk to intermediate-risk warrants ending surveillance.

In 2016 we reported a prognostic model for newly diagnosed prostate cancer by optimising the use of baseline clinicopathological variables (PSA, Grade Group and clinical stage) to estimate prostate cancer mortality (PCM) [8-9]. The Cambridge Prognostic Group (CPG) 5-strata model has been tested in over 86,000 men and consistently outperformed the NICE/EAU prognostic model, regardless of treatment type and patient age [9]. In this model we identified a sub-stratum of intermediate-risk cancer with low rates of PCM (CPG2) and a group with more lethal outcomes (CPG3) [8-9]. These sub-groups correspond to the 2017 updated risk model revisions endorsed by the AUA/ASTRO/SIU guidelines and designated as “favourable” and “unfavourable intermediate-risk” respectively [10].

Here we explored if using the CPG sub-classification of intermediate-risk could identify men with different benefits from immediate radical therapy versus initial surveillance. If so, this could be used to define which intermediate-risk men could be surveyed and specific criteria for AS discontinuation to inform tailored follow-up protocols. To do this we exploited different datasets (i) Longitudinal population datasets from UK and Sweden to compare relative mortality reductions from radical therapy over conservative management stratified by the CPG criteria and (ii) Contemporary AS cohorts from UK and Spain optimally characterised for true disease burden at the point of AS entry by magnetic resonance image (MRI) guided biopsies to test the use of the CPG groups for stratifying follow-up.

Methods

Cohorts

Population cohorts to assess treatment vs. non-treatment related prostate cancer mortality

The CPG model was developed and validated as previously reported [8]. For this study we reanalysed the PCM outcomes from men in the first 3 groups (CPG1-3) defined as – **CPG1**: Grade Group (GG) 1 AND PSA < 10 ng/ml AND Stages T1–T2, **CPG2**: GG 2 OR PSA 10–20 ng/ml AND Stages T1–T2, **CPG3**: GG2 AND PSA 10–20 ng/ml AND Stages T1–T2, OR GG3 AND Stages T1–T2 AND PSA < 20 ng/ml (Table 1). These groups were studied in the following cohorts:

UK East of England cohort: A cohort of men with primary prostate cancer (ICD10 site: C61), diagnosed in the East of England Cancer Network (United Kingdom) area and registered by the Public Health England National Cancer Registration Service – Eastern Office (NCRS(E)) was assembled as previously reported 8. All data were anonymized at source in the NCSR(E) before being used for analysis, and as a result no formal ethics review was deemed necessary.

Prostate Cancer Data Base Sweden: The Prostate Cancer Data Base Sweden (PCBaSe) 3.0 was created through record linkages between the National Prostate Cancer Register (NPCR) of Sweden and nationwide health care registers and demographic databases and has been previously described 11-12. Ethical permission was provided by the Research Ethics Board at Umeå University, Sweden.

From both cohorts we identified men diagnosed between 2000 and 2010, with no evidence of metastatic disease (Mx or M0), aged <80 years and followed until death, emigration, or censorship (31st December 2015 for PCBaSe and 30th September 2013 for UK East of England), whichever occurred first. The median follow-up was 7.0 years (52% with 10 years or more follow up) in PCBaSe and 6.9 years (49% with 10 years or more follow up) in the UK East of England cohort. The outcome event for each man was one of the following: alive or prostate cancer specific death. Individuals who

died of other causes was excluded to remove the effect of other cause mortality for this comparison. Each man was assigned a CPG group with only those in CPG 1-3 studied further for this analysis. The webtool is available at http://cambridgeprognosticgroup.com. Only subjects with all components of diagnostic stage, primary and secondary grade and presenting PSA (ng/ml) as well as data on follow up and survival were included as these variables were essential for the study. Any cases where these data were missing were not included. To investigate differences in PCM, we further sub-divided men in CPG2 and CPG3 by whether they were coded as being treated by primary radical therapy (prostatectomy or radiotherapy) or by the term conservative management. Men in CPG1 (similar to NICE and AUA defined low-risk) were used as the baseline comparator.

Predicting progression and stratifying follow up on AS

To explore factors that might predict the development of poorer prognosis disease we used a contemporary cohort of men on AS in our institution who had their disease burden optimally characterised by image-guided targeted and sectoral biopsies at the start of surveillance. The cohort, follow-up and outcomes have been previously described as was the institutional board approval (Cambridge University Hospital Trust, Cambridge, UK; registration number: 3592) [13]. Our standard diagnostic pathway was an initial 12-core sectoral transrectal prostate biopsy. A baseline mpMRI was performed at AS entry with the mpMRI used to then guide a subsequent early transperineal re-biopsy performed using image-fusion software [13]. Where no lesion was identified, standard sectoral biopsies were performed. A reported lesion (of ≥3 on the Likert scale) was considered MRI positive. The only exceptions were men who had already had previous negative biopsies or those first diagnosed using a transperineal image-fusion method. This cohort thus had as accurate as possible characterisation of the actual disease burden at the start of AS to reduce/eliminate risks of misclassification and hence detect the true rates of disease progression. Briefly, included for this study were men under 80 years with clinical stage T1-T2, PSA≤20ng/ml, histological Grade Group ≤2,

a composite CPG criterion of 1 or 2 at entry, data on MRI prostate volume and derived PSA density and a minimum of 12 months follow up. All men had similar planned follow up with 3-monthly PSA testing, annual repeat mpMRI and scheduled protocol interval re-biopsies as previously reported 13. To re-test the finding we sourced an independent cohort from Spain (Valencia). This study was conducted under institutional review board approval (Ethics committee title: CAPROSIVO) and with a median follow-up of 2.9 years. This cohort included similar patients with the exception that Grade Group 2 was only allowed in men ≥ 70y and the PSA limit was up to 10 or PSAd < 0.20 if prostates were bigger than 60cc. As before a baseline mpMRI was performed at AS entry or before a repeat confirmatory biopsy if the diagnostic biopsy was a non-image guided 10-12 cores TRUS-guided biopsy. AS was only used if the image guided confirmatory biopsy continued to meet the inclusion criteria.

Statistical analysis

The first analysis involved comparing the prostate cancer mortality (PCM) rate of men treated initially by radical therapy or conservative management and stratified by CPG criteria. The 10-year cumulative PCM rate was calculated for men in CPG2 and CPG3 and who were either treated or managed conservatively and compared with the PCM in for men in CPG1 (classical low-risk disease and used as the baseline comparator). The analysis was performed using lifetable command in STATA statistical package (STATA 15). In the second analysis, we explored predictors of progression to CPG3 in a contemporary AS cohort. For this analysis the variables considered included only data which would be available at baseline AS entry, namely CPG criteria, MRI lesion presence and PSA density (PSA divided by MRI defined tumour volume). To assess correlation between each predictor and progression to CPG3, we computed the Phi Correlation Coefficient, which is designed to measure the degree of relation for two variables which are binary. Comparisons of progression distribution were made using the Freeman-Halton extension of Fisher's exact test to compute the

(two-tailed) probability. Predictive test statistics were derived by calculating the true and false positive/negative rates. A multivariable model was not deemed statistically valid for this analysis given the relatively low number of events. A p value of <0.05 was used as a significance threshold.

Results

Comparison of 10-year cumulative PCM for men in CPG2 and CPG3 with versus without treatment

The final UK cohort included 3659 men, of which 1299 were in CPG1, 1413 in CPG2 and 947 in CPG3 cancer. Amongst men in CPG2, 477 were managed conservatively and 936 received radical therapy. The corresponding numbers in CPG3 were 179 and 768 respectively (Table S1). The 10-year cumulative PCM amongst men in CPG1 was 2.3%, consistent with the known excellent survival in men with low-risk disease 6. PCM in men with CPG2 was low whether managed by conservative management or radical treatment (3.5% versus 1.5%). The men who had treatment for a CPG3 cancer had also a very low PCM of 1.9%. (Figure 1). In contrast, men in CPG3 who were managed conservatively had a nearly 4-fold higher PCM (8.3%) compared to untreated men and indeed to any other group. The final cohort from the PCBaSe database included 27,942 men with 15,477, 8495 and 3970 men in CPG1, 2 and 3 respectively (Table S2). In this cohort the cumulative 10-year PCM was 1.0% in CPG1, 2.7% in CPG2 untreated and 2.2% in CPG2 treated men. In contrast, untreated men with CPG3 had a 10-year PCM of 12.5%, twice as high as the mortality in CPG3 men who had initial radical therapy (6.1%) (Figure 2).

Using CPG criteria to determine predictors of progression

Our results suggest a clear advantage from radical therapy in men with CPG3, but only a minimal advantage for those with CPG1 or CPG2. This suggest that progression to CPG3 might be a valid criterion for switching to treatment. We asked if this criterion could be used to identify predictors of progression at AS entry. Data from 133 men in a contemporary AS cohort with a median follow up of

3.5 years were used for this analysis. The attributes of the cohort and CPG assignments are shown in Table 2. A key advantage of this cohort for this analysis was the comprehensive up-front disease characterisation using image-guided re-biopsy allowing the assessment of the true rates of disease progression. In this cohort 22 men had evidence of progression during follow-up, but only 8 progressed to CPG3 (6%). For predictors we focused on attributes available at the point of diagnosis. PSAd (cut-offs used were 0.10, 0.15 and 0.20 ng/ml/cm3), mpMRI positivity (Likert score of 3-5), CPG group at entry, biopsy core involvement and family history (first degree family member dying of prostate cancer) (Table 3). Correlation statistics showed that the key predictors of progression to CPG3 were a PSAd ≥0.15 (p=0.006), PSAd ≥0.20 (p<0.0001) and CPG2 disease at diagnosis (p=0.02). The presence of an MRI lesion itself was not overall a predictor of progression. To explore this further we stratified the cohort by mpMRI positivity. PSAd and CPG were equally predictive of progression whether or not there was an MRI lesion (Table S3). Men with an MRI positive lesion and a PSAd <0.15 however had a trend to a greater risk of progression (2/52, 3.8%) compared to men with a negative scan (0%) but this did not reach statistical significance.

Stratified tiers of follow up based on progression risk

These data were used to construct three surveillance follow-up tiers based on CPG and PSAd at diagnosis: **Tier 1** CPG1 and PSAd<0.15, **Tier 2** CPG2 OR PSAd≥0.15 and **Tier 3** CPG2 AND PSAd≥0.15. Table 4A shows the percentage of men progressing in each tier along with the proportion of patients they represent in the UK cohort of 133 men. In brief 1%, 8% and 21% of men in Tiers 1,2 and 3 progressed respectively (Negative Predictive Value of 99%). Men in the highest risk tier represented only 14% of the cohort whereas men in the lowest tier represented the majority (55%) of the cohort. We also modelled the use of these tiers if any pathological progression was used as the endpoint. Here the incidence of progression again showed a stepwise increase being lowest in men in tier 1 (9%) and highest in tier 3 (26%) (Table S4A). We re-tested this strategy in an external cohort from

Spain of 143 men. The baseline characteristics of this cohort are shown in Table S5. In this cohort 23 progressed but only 8/143 (5.5%) progressed to CPG3. Here the 3 tiers again identified different rates of progression to CPG3 with only 3% of men in Tier 1 progressing versus 14% of men in Tier 3 (Negative Predictive Value of 97%) (Table 4B). Men in the highest tier represented only 5% of the cohort whereas men with the lowest risk (Tier 1) represented the majority of the cohort (68%). When any pathological progression was used as an endpoint, the model again showed utility with the incidence of progression being 10% in Tier 1 and 43% in Tier 3 (Table S4B).

Discussion

AS for early prostate cancer is an established management modality for early prostate cancer [2, 14-15]. The use of MRI and image-guided biopsies has also increased confidence that high-grade cancers are less frequently missed at AS commencement and reduced the anxiety of surveying men [16-17]. With this increasing demographic, there is an imperative need to define which men are unsuitable for AS, rationalise follow-up and have well-evidenced hard stops. This has been notoriously difficult to achieve with a multitude of different guidelines, recommendations and no randomised trials [3, 18].

An increasing body of evidence suggests that men with intermediate-risk disease may do very well from a non-interventional strategy [19-21]. Indeed, the current definition of intermediate-risk has been questioned with many cancers being designated Gleason sum 3+4 (Grade Group 2) instead of 6 (following revisions to the ISUP grading system in 2005) without any material change in clinical outcomes [22-23]. Nevertheless, there remains controversy about AS as a strategy in men with intermediate-risk features. Data from the Toronto group suggest that men with Gleason sum 3+4 (Grade Group 2) disease have a higher risk of metastasis compared to men with Gleason 3+3 disease (Grade Group 1) [24]. The Vancouver group however showed that men with favourable

intermediate-risk disease had similar treatment conversion rates compared to men with low-risk disease [25]. The Canary Foundation PASS study also did not find significant association between baseline risk group and final radical prostatectomy pathology in men initially managed by AS [26].

Our recent work has explored the innate heterogeneity within the traditional intermediate-risk classification and shown 2 distinct sub-groups with very different mortality and metastatic risks [8-9, 27]. In this study we put this sub-classification to the test by comparing the PCM in men managed by either immediate radical therapy or conservative means. In a UK and a Swedish population cohort, together including over 31,000 men, we observed that a survival benefit from upfront radical treatment was evident only in men with CPG3 disease with an up to 4-fold reduction in PCM rates. These results are caveated by the fact that both populations were retrospective, non-randomised, did not strictly use AS (as it is currently known) and was inevitably likely subject to selection bias at initial treatment allocation. Nevertheless, the results mirror many other studies which have shown that unfavourable intermediate-risk disease (CPG3) is associated with a poorer outcome from AS compared to favourable intermediate-risk (CPG2) [25,28]. They are also consistent with results from the randomised ProtecT trial and other studies whereby the majority of men had low-risk or favourable intermediate-risk disease without survival differences between treated and untreated men [6,29]. While this paper was in preparation a multi-centre study from the US further showed that the distinction between favourable intermediate-risk (CPG2) and unfavourable intermediate-risk disease (CPG3) also has utility in distinguishing men with different risks of metastasis after radical treatment [30]. Although AS was not explored in this study, it showed a starkly higher risk of metastasis at 10 years in men with CPG3 disease (10-13.5%) compared to CPG2 (0.2-3.5%) depending on the type of radical treatment. This study also, unsurprisingly, showed very different rates of prostate cancer mortality with results remarkably similar to our own findings [30]. Based on this, it would seem reasonable that progression to CPG3 is a pragmatic trigger to end AS and switch to treatment. Conversely, progression from CPG1 to CPG2 or within CPG2 parameters may not

materially affect prognosis. These data reinforce the fact that men with CPG3 should not be offered AS in the first place and also give reassurance that men with CPG2 disease can be safely offered surveillance. This could then help reduce variability and standardise National and International guidelines on AS as most do not use sub-divisions of intermediate-risk in their recommendations (3)

Establishing a prognostically relevant trigger to end AS allows a pragmatic approach to defining risk factors for progression. To investigate this, we used two contemporary AS cohort that were optimally characterised at baseline with MRI-guided biopsies. A key attribute of the cohorts we have used here are the fact that early disease mis-classification was reduced as much as possible by early repeat image-guided biopsies. Short of removing the prostate for histological examination, it is as accurate as currently possible in determining correct risk assignment at the start of AS and hence allows a true measure of the rates of disease progression on AS especially in the short to medium term [31-32]. In these cohorts, progression to CPG3 occurred in only 6-8% of men over 3 years. The key predictors of progression were a high PSAd and CPG2 disease at the outset. It would be intuitive that starting with intermediate-risk disease confers a higher progression risk. Strikingly however, many men with CPG2 disease (32/37 in the UK series, >85%) actually did not progress. PSAd has been well reported to be a marker of progression in AS [33-35]. Remarkably the threshold value of 0.15 has been found independently in many of these studies [33-35]. In our analysis the presence of a baseline MRI lesion was not predictive of progression and we had too few cases to sub-analyse differences between Likert 3, 4 and 5 lesions. We did observe that men with a low PSAd and a positive MRI had higher progression rates compared to those with a negative scan. MRI positivity may still be an important factor but our data was under-powered to identify it, alternatively, it might have specific value when the PSAd is low. Other studies have shown the value of adding mpMRI to guide repeat biopsies and improve grade reclassification though its role in monitoring remains keenly debated [32, 36-38]. Clearly though, using mpMRI as part of AS seems logical and a guide to trigger repeat biopsies though not necessarily a change in management [13].

These insights allow us to propose a 3-tiered follow-up strategy applicable at the point of AS entry (Table 5). In this model the majority of men in AS (CPG1 and PSAd<0.15) could have long interval follow-ups. Conversely, the model also allows men at the top ends of inclusion (CPG2 and high PSAd) to also be monitored but with a closer regime. In our AS cohorts these men constituted only 5-14% of men. In comparison to a non-stratified approach our regime significantly reduces the need for out-patient review, imaging and biopsies for the majority of patients [3]. As an example, over 3 years our protocol would reduce out-patient visits alone by >50% compared to the current UK NICE guidelines [39]. Changes in the risk factors parameters during AS can also be used to revise the follow-up strategy as needed. For example, an increase to CPG2 or a higher PSAd may mean men are moved to a more intensive surveillance regime. Although baseline MRI itself was not overall correlated with progression to CPG3, it seems prudent that the presence of a lesion mandates a sooner repeat scan than in men with a negative scan (Table 5). Men should have at least 10 years Life Expectancy (LE) to be suitable for AS let alone be entered into this stratified model. We therefore propose that LE should be assessed at inclusion into the model, when a man is moved up to a higher tier or at the end of a 3 year cycle. Men with a LE of less than 10 years should be considered instead for watchful waiting with PSA and symptom monitoring only.

There are limitations to this study and we consider our findings the basis for further testing and validation. Our prognostic outcomes were based on PCM as we were unable to model the impact on metastatic progression. However, it is unlikely that patients will progress undetected to metastasis on AS without first developing at least CPG3 disease. Indeed, we have previously shown that men in CPG1 and CPG2 never have de novo metastasis when identified using image-based diagnostics [27]. We did not compare the use of the CPG crterios to simply using Grade Groups alone in this study. Guidelines on risk-based management however never only use Grade as a criterion and always use a composite of PSA, Grade and Stage (AUA, NCCN, EAU, NICE). Moreover, we have previously seen in our 2 reports on the CPG model development and validation that men with GG2 and a high PSA have

similar outcomes to men with GG3 and low PSA [8-9]. For these reasons we feel that it is the composite score which is most relevant to clinical practice and AS management. Conservative management in our population datasets were not strictly AS cohorts as defined in the modern era as this term was not generally used in the early years nor was its definition standardised. However, if anything we would expect even better rates of survival in contemporary well characterised (though imaging and targeted biopsies) AS cohorts. Our studies did not find an association with biopsy core involvement which may be a true finding or a technical issue with how biopsies are reported. Of note, out of the 16 AS guideline protocols in a recent comprehensive review, only half mention core involvement and all used different thresholds [3]. MRI targeting has also changed the meaning of biopsy core information and it is currently unknown how this informs AS progression. Our cohorts were small and predominantly white European men but future work in multi-centre and multi-ethnic studies can also investigate the complimentary role of family history, race, testosterone levels and genetic factors in predicting progression [40]. Finally, all our cohort follow-ups were relatively short and extrapolation to longer term follow-up awaits future studies. However, all AS regimes involve iterative change depending on regular re-assessments. We similarly propose that our suggested follow-up forms the basis of a 3-year cycle at which point patients can be reclassified to CPG3 and end AS, moved on to a more stringent follow-up bracket or indeed remain in status quo. Finally, this model was built on the premise of using CPG3 or unfavourable intermediate-risk as endpoint but this may seem too risky for some clinicians to adopt. We did however also observe that the tiers did identify different risks of progression when any clinic-pathological progression was used as an endpoint.

In summary, we present here a pragmatic approach to AS by using disease prognosis to guide inclusion, follow-up and surveillance discontinuation. Our data suggests that men with CPG2 (favourable intermediate-risk disease) can be safely offered AS albeit with a closer follow up regime. We further show that unless a man progresses to CPG3 (unfavourable intermediate-risk disease)

then there is little added survival benefit in conversion to active treatment if AS was selected as an initial management option. Important diagnostic predictors of progression are the baseline prognostic group and PSA density. Together with MRI positivity, these can be used to stratify follow-up regimes with men with CPG1 (low risk disease) eligible for low intensity surveillance. Our results now need further testing in prospective multicentre trials to test their veracity in rationalising AS management without either compromising detection of significant progression or unnecessarily over-monitoring men.

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Additional information

Ethics approval and consent to participate

All data from cohorts in this study were fully anonymised before used and did not need ethics or were collected under the appropriate regulatory approval (see text in methods for each cohort).

Consent for publication

All authors give consent for publication

Availability of data and material

Surveillance cohort data can be accessed by direct application to the study team. Due to legal restrictions, data used for this study have not been made available in the paper or supplemental files and are held by the Public Health England, National and by the Swedish Cancer Registry and can be accessed by direct application to these bodies.

Conflict of interest

All authors confirm that they have no conflicts of interest

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Authors contribution

VJG- incepted and designed the study and analysed data

TB - data acquisition

VT- data acquisition

DT - data acquisition

JRB – data acquisition

JDE - data acquisition

OB - data acquisition

PS - data acquisition

KM – statistical analysis

AL - statistical analysis

All authors – manuscript drafting, critical review and approved final submission

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Cambridge Prognostic Group (CPG)	Criteria
1	Gleason score 6 (Grade Group 1) **AND** PSA < 10 ng/ml **AND** Stage T1–T2
2	Gleason score 3 + 4 = 7 (Grade Group 2) **OR** PSA 10–20 ng/ml **AND** Stage T1–T2
3	Gleason score 3 + 4 = 7 (Grade Group 2) **AND** PSA 10–20 ng/ml **AND** Stage T1–T2 **OR** Gleason 4 + 3 = 7 (Grade Group 3) **AND** Stage T1–T2
4	One of Gleason score 8 (Grade Group 4) **OR** PSA > 20 ng/ml **OR** Stage T3
5	Any combination of Gleason score 8 (Grade Group 4), PSA > 20 ng/ml or Stage T3 **OR** Gleason score 9–10 (Grade Group 5) **OR** Stage T4

Table 1 – Criteria of the Cambridge Prognostic Groups for non-metastatic prostate cancer.

	Active Surveillance cohort n=133
Median age (range) years	63 (46-76)
Median prostate volume (range) mls	51 (20-148)
Median PSA (range) ng/ml	6.4 (0.6-16.6)
Median PSA density (range) ng/ml/cm^3	0.12 (0.02-0.42)
MRI positive (Likert 3-5)	73
MRI negative	60
Cambridge Prognostic Group at entry	
CPG1	96
CPG2	37
Grade Group at AS entry	
Grade Group 1 (3+3)	122
Grade Group 2 (3+4)	11
Median follow up (range) months	39 (15-63)
Active Surveillance status at last follow up	
Ongoing	110
Pathological progression	16
MRI progression	5
PSA progression	1
Died of other causes	1
Progression to CPG3	8

Table 2 – Cohort profile of the men on active surveillance from UK included in the analysis to assess baseline attributes associated with progression to CPG3.

Variable	Pearson chi square	p value
Family History*	1.35	0.25
MRI lesion (≥ Likert 3)	0.2	0.66
CPG2 at diagnosis	5.1	0.02
PSAd ≥ 0.1	1.6	0.20
PSAd ≥ 0.15	7.4	0.006
PSAd ≥ 0.20	17.6	<0.0001
Percentage core positive ≥ 25%	2.4	0.12
Percentage core positive ≥ 33%	0.3	0.58
Previous negative biopsy	3.8	0.29

Table 3 – Analysis of correlation with baseline variables at diagnosis and progression to CPG3 (*1st degree relative died of prostate cancer)

Criteria	Numbers progressed (%)	Cohort numbers out of 133 men (%)
CPG1 **AND** PSAd<0.15	1/73 (1)	73/133 (55)
CPG2 **OR** PSAd ≥ 0.15	3/41 (8)	41/133 (31)
CPG2 **AND** PSAd ≥ 0.15	4/19 (21)	19/133 (14)

A

Criteria	Numbers progressed (%)	Cohort numbers out of 143 men (%)
CPG1 **AND** PSAd<0.15	3/98 (3)	98/143 (68)
CPG2 **OR** PSAd ≥ 0.15	4/38 (10)	38/143 (27)
CPG2 **AND** PSAd ≥ 0.15	1/7 (14)	7/143 (5)

B

Table 4 A: Risks of progression to CPG3 in the UK cohort (n=133) using 3 categories defined by CPG score and PSA density (PSAd). These criteria identified 3 distinct groups with different rates of disease progression **B**: Applying the stratification in an external cohort from Valencia (Spain) (n=179) using the progression classifiers showed similar stratified rates of progression.

Surveillance Group	Inclusion criteria	Suggested follow up
1 **Low Intensity**	CPG1 PSAd<0.15 LE 10 years*	3-6 monthly PSA 18 monthly out-patients MRI at 3 years (no lesion) MRI at 18 months (lesion seen) No routine re-biopsy Triggered re-biopsy if any change
2 **Moderate Intensity**	CPG2 **OR** PSAd ≥ 0.15 LE 10 years	3-6 monthly PSA 12 monthly out-patients MRI at 18 months (no lesion) MRI at 12 months (lesion seen) Re-biopsy at 3 years Triggered re-biopsy if any change
3 **High Intensity**	CPG2 **AND** PSAd ≥ 0.15 LE 10 years	3-6 monthly PSA 6 monthly out-patients MRI at 12 months Re-biopsy at 2 years Triggered re-biopsy if any change

Table 5 – Suggested integrated use of the CPG groups, PSA density (PSAd) and MRI positivity in structuring stratified follow up in AS using progression to CPG3 as the endpoint. The model assumes all men have optimal upfront diagnostics with image guided biopsies. The follow up can be reviewed at 3 years and repeated with patients continuing in the same or a higher surveillance group if needed. Use of biopsy core positivity and MRI lesion score can be used to adapt the strategy (Currently data on their impact on AS outcome and prognosis remains to be tested). * Life expectancy (LE) should be at least 10 years. If LE is <10 years then it is more appropriate for a watchful waiting strategy. LE should be assessed at inclusion, any progression or at the end of a 3 - ear cycle to determine if ongoing AS/switch to treatment is appropriate or if the patient should change to watchful waiting

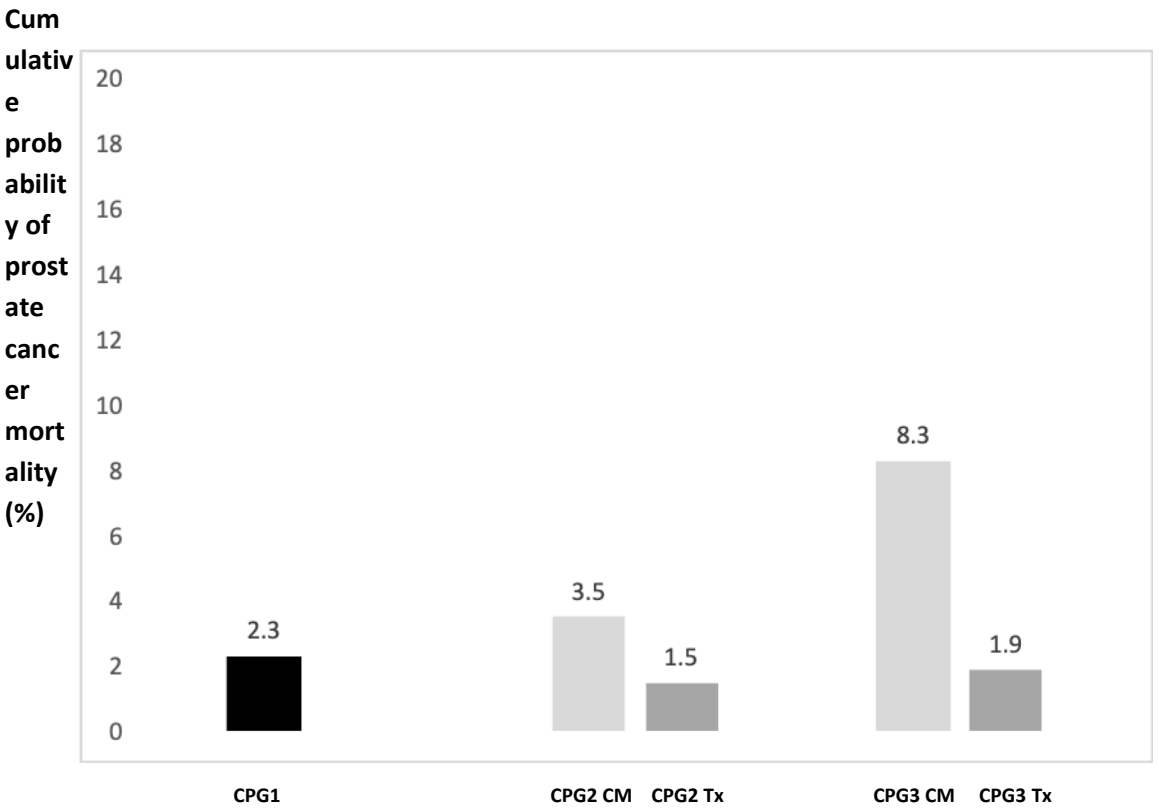

Figure 1 – Cumulative probability of **Prostate Cancer Mortality** at 10 years for men in each of Cambridge Prognostic Group (CPG) 2 and 3 and whether they were managed conservatively (CM) or by radical therapy (Tx) in the UK cohort (n=3659). Comparison is made with outcomes in men with CPG1 (low-risk) disease.

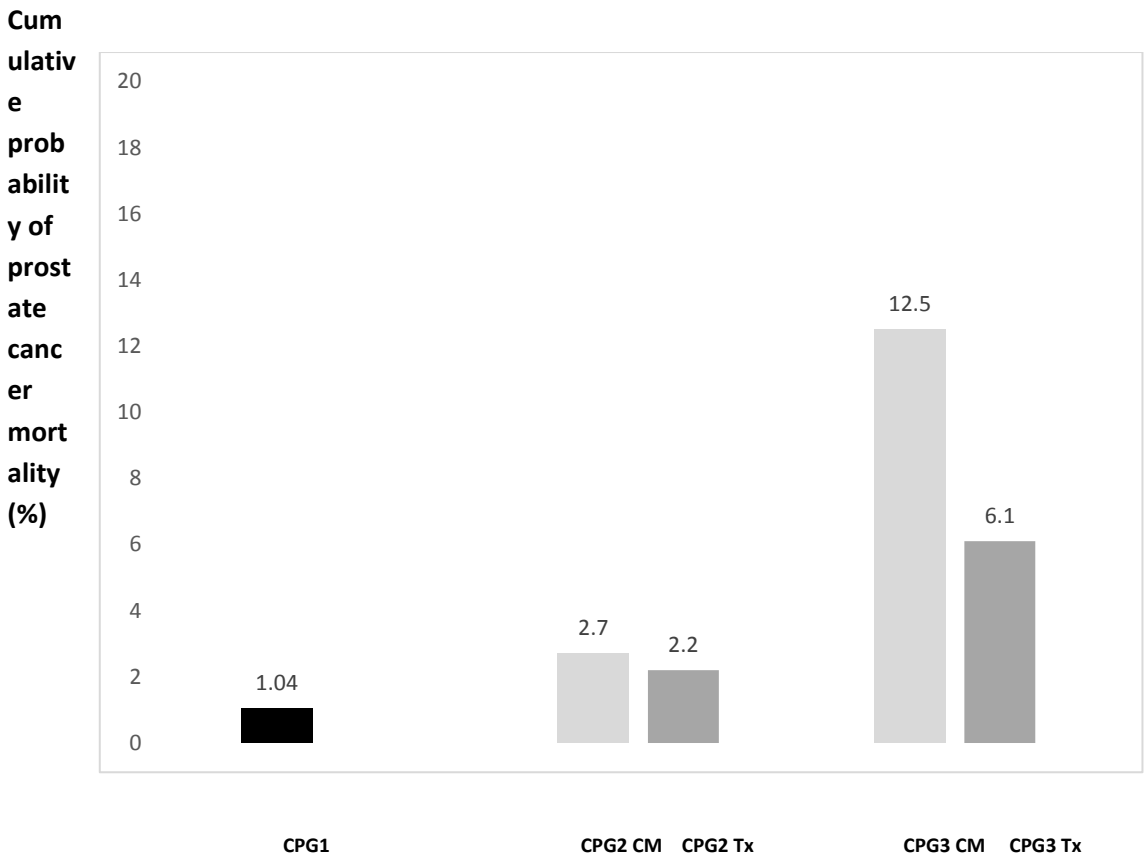

Figure 2 – Cumulative probability of **Prostate Cancer Mortality** at 10 years for men in each of Cambridge Prognostic Group (CPG) 2 and 3 and whether they were managed conservatively (CM) or by radical therapy (Tx) in the Swedish PCBase cohort (n=27,942). Comparison is made with outcomes in men with CPG1 (low-risk) disease.