An improved clinical risk stratification system to better predict cancer specific mortality at diagnosis in primary non-metastatic prostate cancer

An improved clinical risk stratification system to better predict cancer specific mortality at diagnosis in primary non-metastatic prostate cancer.

Vincent J Gnanapragasam[1*#], Artitaya Lophatananon[2*], Karen A Wright[3], Kenneth R Muir[4], Anna Gavin[5] and David C Greenberg[3*].

[1] Academic Urology Group, University of Cambridge, UK, [2]Division of Health Sciences, University of Warwick UK, [3] Public Health England, UK, [4] Institute of Population Health, University of Manchester, UK [5] Northern Ireland Cancer Registry, UK

Academic Urology Group
Department of Surgery
University of Cambridge

Introduction

- It is estimated that the number of new cancer diagnosis in the UK alone will approach 70,000 per annum by 2030, Of this population over 80% will be men presenting with non-metastatic disease.
- Risk stratification is the cornerstone of management for these men. The most widely used stratification system is the 3 strata D'Amico classification first described in the late 1990's (5). It is now clear that within these standard groupings there exists significant heterogeneity in outcomes (9-10). This development is particularly welcome as work from our own centre and others have shown significant grade inflation in contemporary cohorts but not necessarily linked to a poorer outcome (12-13).
- A novel approach to risk sub-stratification was recently reported by the EMPACT group in high-risk surgically treated prostate cancer (16). This work demonstrated that better and poorer performing sub-groups could be identified by considering the number of prevalent high-risk factors an individual had.
- In this current study we explored if this notion could be applied in other risk categories and in the context of predicting prognosis in a primary diagnosis population. We also considered the impending changes in the pathological reporting system in the updated WHO guidelines 2016.
- Our goal was to test whether a new clinical risk stratification model could be developed which would provide a better predictive model for prostate cancer specific mortality (PCSM) at the point of first diagnosis.

Patients and methods

- *Cohorts :* Primary prostate cancers (ICD10 site: C61) diagnosed in residents of the East of England Cancer Network area between 2000 and 2010. Cases with any metastatic involvement were excluded. The median follow up was 6.9 years for the primary cohort. 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.The final primary cohort used for testing and training sets comprised 10,139 subjects with 789 prostate cancer deaths and 2610 overall deaths. To validate the results we sourced an available independent dataset from the Northern Ireland Cancer Registry This validation cohort comprised 1706 subjects with 43 prostate cancer deaths, 144 all cause deaths.

- *Statistical analysis* : Risk groups were initially assigned as low, intermediate and high-risk based on the UK (NICE) guidelines The individual variables used to define the groups (PSA level, the Gleason pathological grade sum and clinical stage) were then used to sub-stratify within each risk category and their association with prostate cancer specific mortality (PCSM). In addition we used the new ISUP prognostic scores as a discriminator. Based on this we derived a new risk stratification system that identified 5 potential outcome groups for PCSM **(Table 1)**. We then used a cross validation method to test and re-test the model by generating a random number seed and then splitting the cohort into 60% (n=6026) as training set and 40% (n=4113) as testing set. To compare survival differences between each risk group, we applied a cox hazards model and the Log rank test with pair-wise comparisons. For visual comparison we used Kaplan-Meier plots. To assess prediction performance, the Harrell's concordance index (CI) was computed. Competing hazards risk regression was applied to include the potential influence of non-cancer deaths and cumulative incidence curves generated and compared between the risk groups (SPSS statistics version 22, STATA/MP 12.1, R Commander plug-in EZR (Easy R) version 1.23 (1) and R version 3.0.1.

New risk group	Criteria
1	Gleason 6 (Prognostic score 1) AND PSA <10ng/ml AND Stage T1-T2
2	Gleason 3+4=7 (Prognostic score 2) OR PSA 10-20ng/ml AND Stage T1-T2
3	Gleason 3+4=7 (Prognostic score 2) AND PSA 10-20ng/ml AND Stage T1-T2 OR GI 4+3=7 (Prognostic score 3)
4	Gleason 8 (Prognostic score 4) OR PSA >20ng/ml OR Stage T3
5	Any combination of Gleason 8 (Prognostic score 4), PSA >20ng/ml, Stage T3 OR Gleason 9-10 (Prognostic score 5) OR Stage T4

Table 1 – Proposed New Prostate Cancer Risk Group criteria. The prognostic scores refer to the new ISUP group grading system.

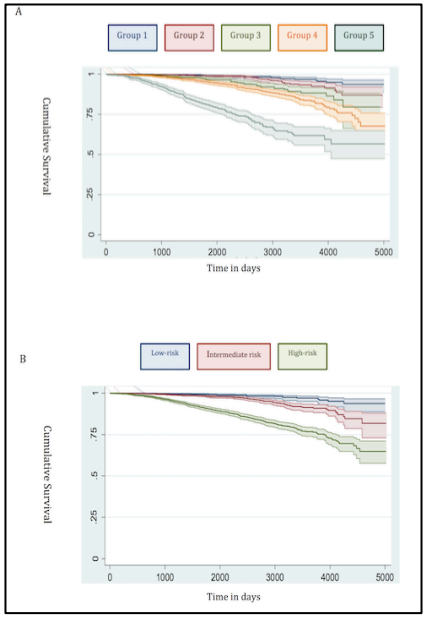

Fig 1 A: New risk criteria applied to training set. B: NICE risk groups applied to training set. Kaplan Meir curves and 95% confidence intervals (shaded areas) are shown for each risk group (n= 6026).

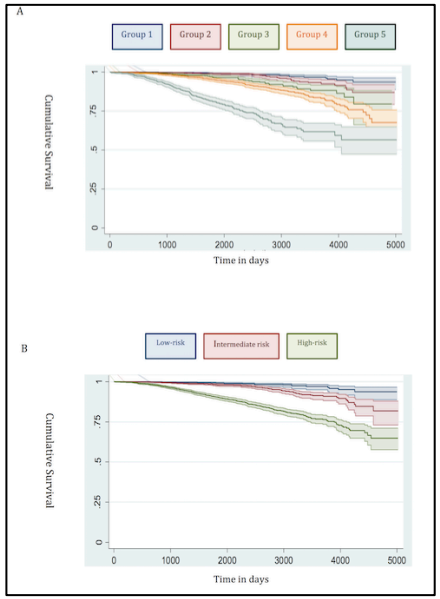

Fig 2 A: New risk criteria applied to testing set. B: NICE risk groups applied to testing set. Kaplan Meir curves and 95% confidence intervals (shaded areas) are shown for each risk group (n= 4113).

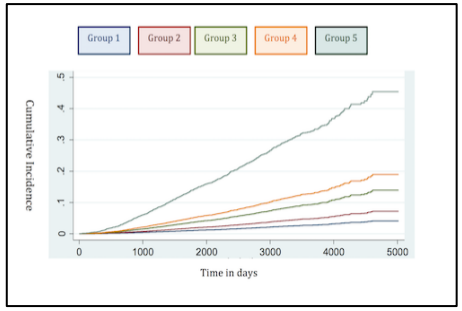

Fig 3: Cumulative incidence curve for the whole cohort to assess competing mortality risk in the new risk model. (n=10,139, 789 prostate cancer death, 1821 other causes) .

New risk group	Sub-hazard ratio	95% CI	p value
1	1	NA	NA
2	1.77	1.16-2.70	0.007
3	3.54	2.38-5.26	<0.0001
4	4.97	3.47-7.12	<0.0001
5	14.34	10.05-20.46	<0.0001

Table 2 – Competing risk regression analysis for the whole cohort (n-10,139) including 789 prostate cancer deaths and 1821 other cause mortality. Comparison of the groups is made with group 1 as the reference.

Cohort (n)	Prostate cancer deaths (%)	Concordance index (confidence interval) NICE	New Risk Group
Testing set (4113)	327 (7.9%)	0.67 (0.64-0.69)	0.75 (0.72-0.77)
Full primary cohort (10139)	789 (7.7%)	0.69 (0.68-0.71)	0.76 (0.74-0.77)
Validation cohort (1706)	43 (2.5%)	0.67 (0.64-0.70)	0.83 (0.80-0.87)

Table 3 – Concordance indices for prostate cancer specific mortality of the NICE risk criteria and the new risk group criteria in testing and full sets as well as the validation cohort.

Summary of Results

- In the entire primary cohort there were 789 prostate cancer deaths within a median follow up of 6.9 years.
- In the training set the new risk system identified distinct subgroups with different risks of PCSM in pair-wise comparison (p<0.0001). Specifically, the new classification identified a very low-risk group (Group 1), a subgroup of intermediate-risk cancers with a low PCSM risk (Group 2, HR 1.62[0.97-2.75]) and a further subgroup with an increased PCSM risk (Group 3, HR 3.35[2.04-5.59]) (p<0.0001) **(Figure 1)**.
- High-risk cancers were also sub-classified by the new risk strata into a better and worse outcome group: Group 4 (HR 5.03 [3.25-7.80]) and Group 5 (HR 17.28 [11.2-26.67]) (p<0.0001) **(Figure 1).**
- These results were recapitulated in the testing set **(Figure 2).**
- In competing risk regression, cumulative incidence curves and sub-hazard ratios continued to demonstrate a good separation in survival outcomes **(Figure 3 and Table 3)**
- Compared to NICE the new risk stratification system demonstrated an improved prognostic concordance index of 0.75-0.76 versus 0.67-0.69 ((p<0.0001). In an external cohort the new system achieved a concordance index of 0.83 **(Table 3)**.

Conclusion

A novel and simple 5 strata risk classification system out-performs the standard 3 strata risk criteria in predicting the risk of PCSM at diagnosis in men with primary non-metastatic prostate cancer.