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

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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 Test diagnosis.

Patients and methods

• Cohorts: Primary prostate cancers (NCI site: G61) 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 and 7,889 prostate cancer specific 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 specific 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 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=6029) 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 (C) 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 [IPSS statistics version 22, STATA/MP 12.1, R Commander plugin in EZR (Easy R) version 1.23 (1) and R version 3.0.1.

<table>
<thead>
<tr>
<th>New risk group</th>
<th>Criteria</th>
<th>Concomittant indices for prostate cancer specific mortality, PCSM at diagnosis in men with primary non-metastatic prostate cancer.</th>
<th>Sub-hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gleason 6 (Prognostic score 1) AND PSA &lt;10ng/ml AND Stage T1-2</td>
<td>NICE</td>
<td>1</td>
<td>NA</td>
<td>0.75-0.77</td>
</tr>
<tr>
<td>2</td>
<td>Gleason 3+4 (Prognostic score 2) OR PSA 10-20ng/ml AND Stage T1-T2</td>
<td>NICE</td>
<td>4.97</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Gleason 4+5 (Prognostic score 3) OR PSA 20-100ng/ml OR Stage T3+</td>
<td>NICE</td>
<td>14.23</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Any combination of Gleason 8 (Prognostic score 4), PSA &gt;20ng/ml, Stage T4</td>
<td>New Risk Group</td>
<td>0.67</td>
<td>0.64-0.68</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OR (Gleason 9-10 (Prognostic score 5) OR PSA &gt;100ng/ml OR Stage T4)</td>
<td>New Risk Group</td>
<td>0.75</td>
<td>0.72-0.77</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Conclusions

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