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## How ‘critical’ is low risk prostate cancer?

### Introduction

Often leaving medical experts bewildered, early stage prostate cancer continues to be a topic of debate with regard to timeous screening and intervention. The majority of affected men with early stage disease will have an excellent life expectancy and a low risk of progression to a life-threatening malignancy<sup>1</sup>. Insurers design critical illness policies with the intention being to cover medical conditions that are likely to have a life-changing impact on the life insured, with payment alleviating financial pressure as recovery and adjustment to an altered way of life take place. Should insurers include lower risk prostate cancer in such products or are they well positioned to exclude these altogether, considering the favourable outcome?

### Background

Prostate cancer is commonly known as the cancer that many men die ‘with’, and not ‘from’, with most types behaving in a biologically indolent manner and thus complicating the decision on best treatment. The prostate-specific antigen (PSA) test, used since the 1980s, has resulted in screening controversy with unnecessary biopsies being performed, over-diagnosis of indolent cancers, and excess morbidity. The implementation of screening programs within developed countries has led to the incidence of prostate cancer being more than double that seen in developing countries and globally this still remains one of the most commonly diagnosed cancers in men<sup>2, 3</sup>. This cancer is unique to insurers in that applicants

may harbour an existing untreated tumour at the time of underwriting and still expect reasonable life cover to be offered. On the other hand, accepting these lower risk cancers as being ‘critical illnesses’ remains a challenge.

In order to best predict how men with localised prostate cancer would respond to treatment (both the risk of mortality and recurrence), risk stratification schemes have been developed based on the PSA level, biopsy Gleason score, and 2002 American Joint Committee on Cancer (AJCC) T-category. Low risk disease can be defined as “PSA  $\leq$  10 ng/ml and a Gleason score of 6 or less and clinical stage T1 or 2a”<sup>4</sup> and while some low risk tumours still result in undesirable outcomes, there is currently no other predictive assessment tool available that can evaluate these low risk prostate cancers more definitively. Intermediate and high risk diseases (having higher PSA levels, Gleason scores and clinical staging) typically involve more sinister tumours with greater risk of rapid spread and ultimate fatality<sup>5</sup> and are already being detected with a high level of accuracy by multi-parametric magnetic resonance imaging (mpMRI) – an emerging predictive diagnostic biomarker test<sup>6</sup>.

<sup>3</sup> Srikanta Banerjee, Aaron Kaviani. International Journal of Clinical and Experimental Medical Sciences. Worldwide Prostate Cancer Epidemiology: Differences Between Regions, Races, and Awareness Programs. © 2016 by SciencePG, Johns Hopkins University, USA, pp. 1-6

<sup>4</sup> D’Amico A.V, et al. JAMA: Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localised Prostate Cancer. © 1998 by American Medical Association Delete, pp. 969-974

<sup>5</sup> See footnote 4

<sup>6</sup> Thompson LC. Australian Family Physician. Multi-parametric MRI in the diagnosis of prostate cancer – a generational change. ©2016 by The Royal Australian College of General Practitioners, Melbourne, Australia, pp. 597-602

<sup>1</sup> Prostate Cancer Foundation of Australia, September 5 2017; What is cancer?

<sup>2</sup> See footnote 1

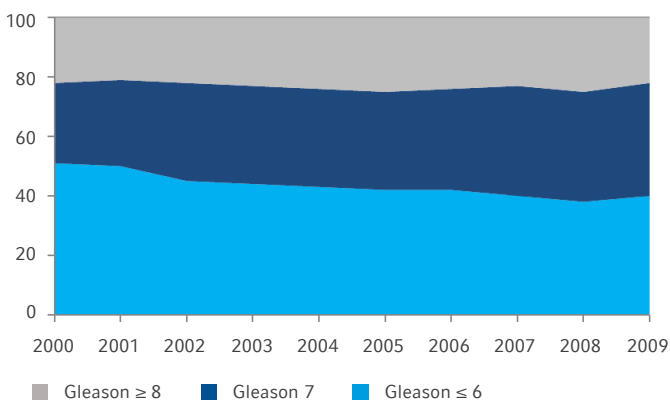
## Gleason score

Described in 1966, Gleason grading has become the cornerstone in the management of prostate cancer<sup>7</sup>. Pathologists assign a grade of 1-5 to prostate cells with 1 being assigned to cells that fully resemble normal prostate cells and 5 being assigned to cells with least resemblance. The Gleason score is useful for predicting how fast a tumour may grow or metastasise and is generally calculated as the sum of the following two allocated histological Gleason grades:

- the commonest grade seen under the microscope, and
- the highest grade identified

Because Gleason grades 1 and 2 are so seldom used for classifying biopsies, the lowest Gleason score for a prostate biopsy specimen is usually 6<sup>8</sup>. These cancer cells closely resemble normal prostate cells that typically grow slowly<sup>9</sup> and are found in 40% of all histological specimens (Figure 1)<sup>10</sup>. More than half of localised prostate cancers (T1-2a) have a Gleason score of 6 or less<sup>11</sup>.

**Figure 1: Proportion of new cases of prostate cancer by Gleason score at diagnosis, where known, 2000-2009<sup>12</sup>**  
in %



<sup>7</sup> Shah Rajal B, Zhou Ming: Pathology International. Recent advances in prostate cancer pathology. Gleason grading and beyond. © 2016 by Japanese Society of Pathology and John Wiley & Sons Australia Ltd, Japan & Australia, pp. 260-272

<sup>8</sup> See footnote 7

<sup>9</sup> American Cancer Society, September 5 2017; Understanding your pathology report.

<sup>10</sup> National Collaborating Centre for Cancer. September 5 2017; Prostate cancer: diagnosis and treatment.

<sup>11</sup> Jun Li, et al.: Prostate Cancer. "Recent Trends in Prostate Cancer Incidence by Age, Cancer Stage, and Grade, the United States, 2001-2007". © 2012 by Jun Li et al, Emory University, USA, pp. 1-8

<sup>12</sup> See footnote 10

A Gleason score of 7 may be summed up as either

- '3 + 4' where the predominant cancer cells are grade 3 and the highest grade identified is grade 4 or
- '4 + 3' where grade 4 represents both the predominant morphological cancer variant as well as the highest grade seen by the pathologist with grade 3 being less commonly seen on the histological specimen.

Due to the different clinical implications of Gleason scores, a new Gleason Grade Grouping system has been proposed by the group from Johns Hopkins Hospital (Table 1) and further differentiates the different Gleason scores<sup>13</sup>.

**Table 1: Gleason Grading of Prostatic Carcinoma<sup>14</sup>**

Grade Group	Gleason Score
1	≤ 6
2	7 (3 + 4)
3	7 (4 + 3)
4	8
5	9 - 10

To add complexity, 40%<sup>15</sup> of men with a Gleason score 7 can be upstaged after prostatectomy to a Gleason score 8 (high risk disease) due to high grade foci being missed in original biopsies. Not only are the clinical implications of a Gleason score 6 different to a score of 7, additional prognostic differences occur with any upstaging of the latter.

## mpMRI

mpMRI, still considered to be in its infancy, has varying results depending on both the radiologist's practical experience as well as associated technical aspects and is by no means a replacement for a prostate biopsy. Used to help distinguish between indolent and clinically significant prostate cancer (and hence guide treatment), it is already considered to be a much more powerful risk stratification tool than the PSA test. While highly sensitive at detecting high Gleason grade cancers, the diagnostic specificity is relatively low. In many countries, National Health Insurance

<sup>13</sup> Gordetsky et al: Diagnostic Pathology. Grading of prostatic adenocarcinoma: current state and prognostic implications. © 2016. Gordetsky and Epstein, University of Alabama, USA, pp. 1-8

<sup>14</sup> See footnote 13

<sup>15</sup> Pedler K, et al. Australian Family Physician. The current status of MRI in prostate cancer. ©2016 by The Royal Australian College of General Practitioners, Melbourne, Australia, pp. 225-230

funds may not typically cover the cost of mpMRI, making it an expensive predictive tool for people without private health insurance, and potentially limiting its application in life insurance<sup>16, 17</sup>.

### Tumour size

Localised disease (where the cancer has not yet spread outside the prostate) corresponds to AJCC stage I and II and constitutes around 80% of all diagnosed prostate cancers with a relative 5-year survival rate of nearly 100%<sup>18</sup>. Despite various treatment options being available for treating early stage localised prostate cancer, there is on-going controversy as to whether any true differences in survival benefits are present. Prostate cancer is considered to be 'clinical T1' when it is clinically unapparent (neither palpable nor visible by imaging). Clinical T1a and T1b prostate cancers are usually discovered at the time of transurethral resection of the prostate (TURP) for a benign enlarged prostate gland and are diagnosed with far less frequency than that seen during the pre-PSA testing era where proportionally much more prostate cancer was diagnosed after the TURP procedure. In a retrospective review of TURP procedures, the incidental prostate cancer rate for T1a-b was < 16% with 90% having a Gleason score of 6 or less. In approximately two thirds of cases, T1a tumours did not receive any active treatment<sup>19</sup>.

T1c is the commonest form of T1 prostate cancer and is specifically defined as a T1 that is found during a needle biopsy, usually because an increase in PSA level had been detected during routine cancer screening. Critical illness policy definitions that include T1c prostate cancers are likely to result in a much higher number of claims because T1c constitutes up to 47% of all prostate cancers<sup>20</sup>. Two thirds of T1c prostate cancers have a Gleason score of 6 or a PSA level < 10 ng/ml and individuals with these low risk prostate cancers could reasonably opt for no active treatment<sup>21</sup>. While low risk disease represents the bulk of prostate cancers and substantially influences premiums, a

proportion could theoretically remain clinically silent throughout a person's life.

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### Treatment of low risk disease

Treatment choice is closely discussed with the individual and takes into account their life expectancy, overall health status, and tumour characteristics<sup>23</sup>. Radical prostatectomy (performed through the open, laparoscopic or robotic assisted technique) can result in urethral strictures, urinary incontinence or sexual dysfunction. However, in 2010 the British Association of Urological Surgeons reported an overall morbidity rate of less than 10%<sup>24</sup>. Radiation therapy is done by means of external beam radiation therapy or brachytherapy and while it does not typically result in urethral strictures, urinary incontinence is seen in < 10% of cases and the 5-year actuarial rate of erectile function preservation has been shown to be 59%<sup>25</sup>. 'Active surveillance' (close follow-up with the intention to cure if disease shows early signs of progression) and 'watchful waiting' (follow-up in men with co-morbidities and lower life expectancy with no intention for curative treatment) are done less frequently but are also appropriate management options.

### Conclusion

Low risk prostate cancer is a key driver of cancer claims and the true clinical (and insurance) significance is an on-going dilemma for both clinician and insurer. Specifically including all T1c prostate cancers within a cancer policy definition will continue to have a substantial impact on the proportion of expected claims. Despite complication rates

<sup>16</sup> Thompson LC. Australian Family Physician. Multi-parametric MRI in the diagnosis of prostate cancer – a generational change. ©2016 by The Royal Australian College of General Practitioners, Melbourne, Australia, pp. 597-602

<sup>17</sup> Pedler K, et al. Australian Family Physician. The current status of MRI in prostate cancer. ©2016 by The Royal Australian College of General Practitioners, Melbourne, Australia, pp. 225-230

<sup>18</sup> American Cancer Society. September 5 2017; Survival rates for prostate cancer.

<sup>19</sup> Brandon Otto, et al: Advances in Urology. Incidental Prostate Cancer in Transurethral Resection of the Prostate Specimens in the Modern Era. © 2014 by Department of Urology, Weill Medical College of Cornell University, USA, pp. 1-4

<sup>20</sup> Hung Arthur Y, et al.: The Cancer Journal. Stage T1c prostate cancer: a heterogeneous category with widely varying prognosis. © 2002 by Lippincott Williams & Wilkins, Houston, USA, pp. 440-444

<sup>21</sup> See footnote 20

<sup>22</sup> See footnote 18

<sup>23</sup> Prostate Cancer Clinical Guideline Update Panel, Thompson I., et al. *Gol: Journal of Urology. Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update.* © 2007 by American Urological Association, USA, pp. 2106-2131

<sup>24</sup> National Collaborating Centre for Cancer. September 5 2017; Prostate cancer: diagnosis and treatment.

<sup>25</sup> Pedler K, et al. Australian Family Physician. The current status of MRI in prostate cancer. ©2016 by The Royal Australian College of General Practitioners, Melbourne, Australia, pp. 225-230

being low, insurers are not yet able to positively predict treatment outcomes for prostate cancer and should continue to consider treatment as being clinically significant and potentially life-impacting. Similarly, accurately identifying which prostate cancers will progress remains a challenge. It is medically reasonable for insurers to consider low risk disease as being sufficiently 'critical' to include within a critical illness product, albeit with an undesirable on-going increase in risk premiums. While the mpMRI is an exciting predictive tool with practical limitations and still requires further development, it is likely that this biomarker will play a more important role in the future for insurers when considering the clinical significance of prostate cancer.

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