

# Modified Gleason Grade of Prostatic Adenocarcinomas Detected in the PLCO Cancer Screening Trial

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**Purpose:** We determined the modified Gleason grade of prostatic adenocarcinomas detected in PLCO to assess grade distribution and compare modified Gleason grades of cancer detected in the intervention arm (organized annual screening) vs the control arm (opportunistic screening).

**Materials and Methods:** Modified Gleason grading was performed in 859 radical prostatectomy cases by a single urological pathologist. We compared the proportion of cases with high grade disease in the screened arm vs the control arm by logistic regression analysis.

**Results:** In the intervention arm a modified Gleason score of 5, 6, 7 (3 + 4), 7 (4 + 3), 8, 9 and 10 was assigned in 3.6%, 43.3%, 39%, 7.4%, 3.5%, 3.2% and 0.1% of cases, respectively. In the control arm a modified Gleason score of 5, 6, 7 (3 + 4), 7 (4 + 3), 8, 9 and 10 was assigned in 3.0%, 35.7%, 46.4%, 7.1%, 5.4%, 1.9% and 0.5% of cases, respectively, after correcting for high grade disease over sampling. A high grade modified Gleason score of 7 or greater was detected in 53% of cases in the intervention arm vs 61.3% in the control arm after correction ( $p = 0.019$ ). The median modified Gleason score was 7 (3 + 4) in each arm.

**Conclusions:** A significant percent of cancers in each arm had a component of high grade disease. The modified Gleason grade of prostate cancers detected by organized annual screening was slightly lower than the modified grade of those detected by opportunistic screening. This is an expected consequence of more intensive screening.

**Key Words:** prostate, prostatic neoplasms, mass screening, neoplasm grading, prostatectomy

## Abbreviations and Acronyms

DRE = digital rectal examination

ISUP = International Society of Urological Pathology

PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

PSA = prostate specific antigen

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Study received institutional review board approval at each participating institution.

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THE Gleason grade of prostate adenocarcinoma is one of the most powerful, if not the most powerful, prognostic indicator for this cancer.<sup>1</sup> Gleason histological grade is associated with all meaningful pathological and clinical outcome end points, and it is routinely used in patient treatment and prediction of the response to therapy.<sup>2</sup> Gleason scoring changed

little from its introduction by Gleason in the 1960s until 2005, when a modified Gleason grading system was proposed at an ISUP consensus conference to reflect changes in clinical and pathology practice.<sup>3</sup> These changes included the designation of poorly formed glands and most cribriform adenocarcinomas as high grade Gleason pattern 4. There was a

slight further modification with all cribriform adenocarcinomas now considered high grade Gleason pattern 4.<sup>1,4,5</sup>

The prostate component of PLCO was performed to determine whether there would be a decrease in prostate cancer mortality by screening with serum PSA testing and DRE.<sup>6,7</sup> PLCO was designed as a test of annual PSA and DRE vs usual care. A total of 76,685 men 55 to 74 years old were enrolled at 10 screening centers between November 1993 and July 2001. They were randomly assigned to the intervention arm (38,340 with organized screening by annual PSA testing for 6 years and annual DRE for 4 years) or the control arm (38,345 with usual care, which sometimes included opportunistic screening). Almost 50% of men in the usual care arm underwent PSA and DRE testing, termed opportunistic. Screening was completed in October 2006. Mortality data were published for this trial<sup>6,7</sup> but to our knowledge modified Gleason grades have not been reported for trial patients with prostate cancer.

We determined the modified Gleason histological grade of prostate adenocarcinoma detected in PLCO in radical prostatectomy tissues to assess the grade distribution. We also compared the modified Gleason grades of cancers detected in the intervention arm (organized annual screening) vs the control arm (opportunistic screening).

## MATERIALS AND METHODS

A total of 2,059 radical prostatectomies were performed between 1994 and 2007 in the PLCO control and intervention arms.<sup>6</sup> Investigators at screening centers obtained written informed consent from each subject and institutional review boards at each participating institution approved the PLCO research protocol. A total of 859 prostatectomies had histological slides available for review, including 693 in the screened arm and 166 in the control arm.

The design of this PLCO study was previously described.<sup>6</sup> Study exclusion criteria were prostatectomy without a Gleason score, a small cell carcinoma component or neoadjuvant therapy. Several representative tumor sections from the dominant tumor nodule in 859 cases were evaluated by a urological pathologist (PAH) blinded to the study arm in which the patient was enrolled. The 2005 ISUP modified Gleason grading scheme<sup>3</sup> was used with the additional slight modification that all cribriform carcinomas were designated as Gleason pattern 4.<sup>1,4</sup> This was a slight modification since in the 2005 ISUP modified scheme most cribriform carcinomas were deemed Gleason pattern 4.<sup>3</sup> Grade assignments were scored as 5, 6, 7 (3 + 4), 7 (4 + 3), 8, 9 or 10. Tertiary grades found in 51 cases were not incorporated into the Gleason score. Patients in the intervention and control radical prostatectomy arms were compared by race/ethnic group, serum PSA at diagnosis, age at radical

prostatectomy, prostatectomy year, and clinical and pathological stage using data from the PLCO clinical database.

Radical prostatectomy tissues obtained for the control arm were known to overrepresent higher grade disease and cancer diagnosed in black men. This was due to the attempt to collect sufficient tissues for these men, who comprised only a small percent of the overall cohort. Therefore, an estimate of true modified Gleason grades in the control prostatectomy population was obtained by stratifying men eligible for tissue collection by race and Gleason score (yes/no black ethnicity and yes/no Gleason score 8-10) and dividing by the number selected in each stratification to provide a correcting weight. These weights were then normalized to the population of 859 men in this study. Differences between the 2 arms were assessed by the chi-square test and logistic regression analysis. The percent of cases in the intervention vs corrected control arms with high grade Gleason score 7 or greater was evaluated using logistic regression analysis.

## RESULTS

The table lists demographics of the intervention and control arms. Most patients in the control and intervention groups were 60 to 69 years old and white/nonHispanic with PSA between 4.01 and 10.00 ng/ml, and clinical and pathological stage II disease. There was no significant difference between the 2 arms in race/ethnic group, serum PSA at diagnosis or clinical stage ( $p > 0.5$ ). Patients in the control arm underwent prostatectomy at a slightly later date than patients in the intervention arm (between 2001 and 2007 in 52.4% vs 44.8%,  $p = 0.013$ ). Patients in the control arm were also slightly older than those in the intervention arm (age 70 years or greater in 25.6% vs 18.5%,  $p = 0.005$ ). Logistic regression also showed slightly significant trends of increasing age at prostatectomy and increasing age at diagnosis in the control vs the intervention arm. The OR for cancer appearing in the intervention arm vs the control arm was 0.968 and 0.952 per year for age at prostatectomy and for calendar year of diagnosis ( $p = 0.029$  and 0.053, respectively).

The table and figure show the distribution of modified Gleason scores in the intervention and corrected control arms. Of cases in the intervention and corrected control arms 89.6% and 89.2%, respectively, were Gleason score 6 or 7. Gleason score 6 comprised 43.3% and 35.7% of cases in the intervention and control arms, respectively. A high grade Gleason score of 7 or greater was assigned in most cases in each arm. A high grade modified Gleason score of 7 or greater was detected in significantly fewer radical prostatectomies in the intervention arm than the control arm (53% vs 61.3%,

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