Limitations in Predicting Organ Confined Prostate Cancer in Patients with Gleason Pattern 4 on Biopsy: Implications for Active Surveillance

Nathan Perlis,* Rashid Sayyid, Andrew Evans,† Theodorus Van Der Kwast, Ants Toi, Antonio Finelli, Girish Kulkarni, Rob Hamilton, Alexandre R. Zlotta, John Trachtenberg, Sangeet Ghai and Neil E. Fleshner

From the Division of Urology, Department of Surgical Oncology (NP, RS, AF, GK, RH, ARZ, JT, NEF), Department of Pathology (AE, TVDK) and Joint Department of Medical Imaging (AT, SG), University Health Network and Division of Urology, Department of Surgery, Mount Sinai Hospital (ARZ), University of Toronto, Ontario, Canada

Purpose: In prostate cancer biopsy Gleason score predicts stage and helps determine active surveillance suitability. Evidence suggests that small incremental differences in the quantitative percent of Gleason pattern 4 on biopsy stratify disease extent, biochemical failure following surgery and eligibility for active surveillance. We explored the overall quantitative percent of Gleason pattern 4 levels and adverse outcomes in patients with low and intermediate risk prostate cancer to whom active surveillance may be offered under expanded criteria.

Materials and Methods: We analyzed the records of patients with biopsy Gleason score 6 (3 + 3) or 7 (3 + 4) who underwent radical prostatectomy from January 2008 to August 2015. Age, prostate specific antigen, Gleason score, quantitative percent of Gleason pattern 4, overall percent positive cores (percent of prostate cancer) and clinical stage were explored as predictors of nonorgan confined disease and time to failure after radical prostatectomy.

Results: In 1,255 patients biopsy Gleason score 7 (3 + 4) was associated with T3 or greater disease at radical prostatectomy in 35.0% compared with Gleason score 6 (3 + 3) in 19.0% ($p < 0.001$). On multivariate analysis for each quantitative percent of Gleason pattern 4 increase there were 2% higher odds of T3 or greater disease (OR 1.02, 95% CI 1.01–1.04, $p < 0.001$). When stratified, patients with Gleason score 7 (3 + 4) only approximated the pT3 rates of Gleason score 6 (3 + 3) when prostate specific antigen was less than 8 ng/ml and the percent of prostate cancer was less than 15%. In those cases the quantitative percent of Gleason pattern 4 had less effect. Time to failure after radical prostatectomy was worse in Gleason score 7 (3 + 4) than 6 (3 + 3) cases.

Conclusions: The quantitative percent of Gleason pattern 4 helps predict advanced disease and Gleason score 7 (3 + 4) is associated with worse outcomes. However, the impact of the quantitative percent of Gleason pattern 4 on adverse pathological and clinical outcomes is best used in combination with prostate specific antigen, age and disease volume since each has a greater impact on predicting nonorgan confined disease. The calculated absolute risk of T3 or greater can be used in shared decision making on prostate cancer treatment by patients and clinicians.

Key Words: prostatic neoplasms, neoplasm grading, prostatectomy, prognosis, watchful waiting

Abbreviations and Acronyms

%GI4 = quantitative percent of Gleason pattern 4
AS = active surveillance
ASCO = American Society of Clinical Oncology
EPE = extraprostatic extension
GS = Gleason score
ISUP = International Society of Urological Pathology
MRI = magnetic resonance imaging
PCa = prostate cancer
PSA = prostate specific antigen
RP = radical prostatectomy

Accepted for publication July 14, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence: Princess Margaret Hospital, Room 3-130, 610 University Ave., Toronto, Ontario M5G 2M9, Canada (telephone: 416-946-2899; FAX: 416-946-6590; e-mail: Nathan.perlis@uhn.ca).

† Financial interest and/or other relationship with GE Healthcare.

0022-5347/17/1971-0075/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.07.076
Vol. 197, 75-83, January 2017
Printed in U.S.A.

In PCa the overall GS predicts adverse pathology findings at RP, biochemical recurrence after treatment and PCa specific mortality.[1–3] GS is also an important determinant of eligibility for AS.[4] Among patients with GS 7 those with primary pattern 4 (GS 7 [4 + 3]) fare significantly worse than those with primary pattern 3 (GS 7 [3 + 4]).[5–8] Higher amounts of pattern 4 carry a higher failure rate.[9] However, whether the exact %Gl4 on preoperative biopsy offers any additional clinical usefulness is uncertain.

Data are emerging that address the added benefit of quantifying %Gl4 on biopsy.[10,11] In a study from Germany in 12,000 men after RP the %Gl4 of RP specimens predicted PSA recurrence free-survival and %Gl4 on biopsy predicted up-staging on the RP specimen.[10] Another study from the University of Michigan identified %Gl4 as a predictor of adverse pathology findings on RP and biochemical recurrence after RP in patients with GS 6-8 on prostate biopsy.[11] The group suggested that GS 7 (3 + 4) PCa with %Gl4 less than 20% carries a low risk of adverse outcomes and, thus, patients could be considered for AS. Supporting that approach, ASCO proposed offering AS to select patients with low volume GS 7 (3 + 4) PCa.[12]

Increasing the pool of patients eligible for AS and avoiding morbidity from radical interventions is appealing but controversial. There is evidence that the presence of any Gleason pattern 4 on biopsy predicts progression in patients on AS.[13] In the Toronto AS cohort with its long followup metastasis developed in 14 of 211 men (6.6%) with intermediate risk PCa vs only 16 of 769 (2%) with low risk disease at a median followup of 6.3 years.[14]

In the current study we explored outcomes in patients who underwent RP and who may have been candidates for extended AS according to ASCO guidelines. Our objective was to determine the relative importance of %Gl4 on biopsy for predicting more advanced disease. Quantifying the risk of adverse pathology findings at RP and failure after RP in this cohort would help infuse real world data into treatment decision making between patients and clinicians.

MATERIALS AND METHODS

Institutional research ethics board approval was obtained for this study. We sought to identify cases that may have been eligible for extended criteria AS. Therefore, data were collected on all patients who underwent RP at University Health Network in Toronto, Ontario, Canada, for biopsy confirmed GS 6 or GS 7 (3 + 4) prostate cancer. Genitourinary pathologists at University Health Network began reporting data on the overall %Gl4 in 2008. As such, cases from January 2008 to August 2015 were included in study. Patients without %Gl4 data were excluded from analysis, as were patients receiving neoadjuvant therapy (radiotherapy or androgen deprivation therapy) or with clinical stage T3-T4 disease. Only the immediate pre-RP biopsy was analyzed.

Gleason grades and scores were assigned using criteria described in the 2005 ISUP modified Gleason system and the further modifications made at the 2014 ISUP Consensus Conference on Gleason Grading.[5,15] The %Gl4 reflects a global percent of all adenocarcinoma present in a given set of biopsies.

The study primary end point was T3 or greater disease on the RP specimen, defined as EPE, seminal vesicle invasion or bladder neck invasion. Univariate and multivariate logistic regression analysis was done to evaluate the association between %Gl4 on the pre-RP biopsy and adverse RP pathology results. Other covariates included were age, preoperative PSA, percent of positive biopsy cores, prostate volume, clinical stage and GS 7 (3 + 4) vs GS 6. We considered %Gl4 as a continuous variable (0% to 49%) and as a categorical variable. Analysis was performed in the entire cohort and stratified between GS 6 and GS 7 (3 + 4) PCa. On multivariate analysis clinical stage and prostate volume were omitted as predictors because of the high amount of missing data. On stratified analysis age, the percent of positive cores and PSA were categorized by median or tertile. The omnibus likelihood ratio and the Hosmer-Lemeshow goodness of fit test were used to determine the overall data to model fit.

As a secondary end point we also examined rates of post-RP failure, defined as time to biochemical recurrence (2 consecutive postoperative serum PSA levels greater than 0.2 ng/ml), adjuvant/salvage radiotherapy or adjuvant/salvage hormonal therapy. Time to event analysis was performed using Kaplan-Meier survival analysis. HRs were calculated using Cox proportional hazard modeling. Statistical significance was considered at 2-sided $p < 0.05$. Statistical analysis was performed with SPSS®, version 22.0 and SAS®, version 9.4.

RESULTS

A total of 1,410 patients with GS 6 or GS 7 (3 + 4) PCa on biopsy were treated with RP. Of these patients 155 were excluded from study due to missing data on %Gl4 in 135 and due to receipt of neoadjuvant therapy in 21. Thus, 1,255 patients were included in analysis (table 1).

The adverse pathology rate in the cohort was 28.6% with a 26.9%, 3.1% and 3.7% rate of EPE, bladder neck invasion and seminal vesicle invasion, respectively. Patients with GS 6 PCa were younger, had lower PSA and were less likely to have palpable disease than those with GS 7 (3 + 4) ($p < 0.05$). GS 7 (3 + 4) on biopsy was associated with a higher rate of T3 or greater at RP compared to GS 6 (35.0% vs 19.0%, $p < 0.001$). When %Gl4 was divided into 5 strata, T3 or greater was more common in patients with higher %Gl4 on biopsy ($p = 0.015$, fig. 1).

Higher %Gl4 on biopsy conferred greater odds of T3 or greater at RP when considered as a