Pathology Review for Patients with Prostate Cancer Referred to the SCCA Proton Center

George E. Laramore, PhD, MD; Jing Zeng, MD; Li-Ming Christine Fang, MD; Jay J. Liao, MD; Kenneth J. Russell, MD

Department of Radiation Oncology, University of Washington Medical Center, Seattle, WA, USA

Abstract

Purpose: Treatment guidelines for patients with newly diagnosed prostate cancer are largely determined by risk stratification (low, intermediate, high), which is based upon 3 parameters: T-stage, prostate-specific antigen value, and Gleason score. The purpose of this report is to evaluate the results of a central review for patients with prostate cancer treated at the center during its first year of operation.

Patients and Methods: Between March 13, 2013, and April 14, 2014, a total of 53 patients with prostate cancer, with Gleason scores initially determined by outside pathologists, were treated at the center. Tissue specimens were obtained for all patients and were reviewed by the Department of Pathology at the University of Washington. The results of this review were tabulated and analyzed.

Results: The original Gleason score was confirmed in 42 cases. The original Gleason score was upgraded in 7 cases and downgraded in 4 cases. Four patients who were originally classified in a low-risk category with a Gleason score of 6 (3 + 3) had a change in Gleason score to 7 (3 + 4). Among patients who were originally classified in an intermediate-risk category via a Gleason score of 7, one was downgraded from (4 + 3) to (3 + 4), while 3 were reclassified in the low-risk category by having a Gleason score of 7 (3 + 4) changed to a Gleason score of 6 (3 + 3). Three patients originally classified as having high-risk disease were reclassified as having intermediate-risk disease upon review. Two patients with initial scores of 8 (4 + 4) had a shift in score to (4 + 3). The greatest change occurred for a patient who was referred with a Gleason score of 9 (4 + 5) but whose Gleason score was shifted to 7 (4 + 3).

Conclusion: Twenty-one percent of patients whose cases underwent review had significant changes in their Gleason scores, which changed their risk category and treatment recommendations.

Keywords: prostate cancer; Gleason score; proton therapy

Introduction

Patients with prostate cancer currently represent a significant fraction of the patients treated at most proton centers presently in operation in the United States. Patients may be referred from a wide geographic area and typically have received their diagnosis from outside physicians by the time they are initially seen at the proton centers. Their prostate biopsies have generally been performed elsewhere and the Gleason scores [1, 2] are determined by pathologists not associated directly with the center or with the physician

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Corresponding author:
George E. Laramore
Department of Radiation Oncology
University of Washington Medical Center
Box 356043
Seattle, WA 98195-6043, USA
Phone: +1 (206) 598-4110
Fax: +1 (206) 598-3498
georgel@u.washington.edu

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group practicing there. The outside pathologists may have varying experience in interpreting the tissue specimen, compared with a pathologist at a major academic center who specializes in genitourinary malignancies. The tumor Gleason score is a key parameter used in assessing a patient's prostate cancer risk profile, which also relies on T-classification and prostate-specific antigen level. Values for these parameters sort patients into low-, intermediate-, or high-risk categories; they also serve as input for various formulae and nomograms that assign the probability of tumor control with various treatments, the probability of distant failure, and the probability of tumor extension outside the prostate gland, and/or spread to the pelvic lymph nodes or seminal vesicles [3–6]. The patient's risk category also determines the extent of the recommended pretreatment evaluation, that is, whether a staging bone scan and/or pelvic imaging with either computed tomography or magnetic resonance imaging should be obtained [3].

For a patient who will be treated with external beam radiation therapy, either photons or protons, the risk category affects decisions on whether to use androgen deprivation therapy (ADT) along with radiation therapy; and if used, the duration of ADT. High-risk patients may be offered ADT for up to 2 to 3 years, while intermediate-risk patients are generally offered a 4- to 6-month course of ADT. Risk category also affects decisions relating to the radiation fields treated, that is, prostate gland alone, prostate gland plus the seminal vesicles, and/or inclusion of the pelvic lymph nodes in the treatment fields. For patients in the intermediate-risk category, the proximal seminal vesicles are generally included in the radiation fields, while the entire seminal vesicles may be treated in high-risk patients [6–10]. Elective treatment of the pelvic lymph nodes is more controversial. There is retrospective evidence that elective irradiation of the pelvic nodes is beneficial for certain patient groups, and many investigators feel that it is appropriate to treat the pelvic nodes when the risk of involvement exceeds 15% [10–14]. A Radiation Therapy Oncology Group trial (RTOG 94-13) initially concluded that in the setting of long-duration ADT, adding pelvic nodal irradiation improved progression-free survival in high-risk patients, but with longer follow-up times this difference disappeared [7, 15]. Nevertheless, the investigators recommended whole pelvic radiation therapy plus long-duration ADT as the "standard of care" for high-risk patients [15]. Elective pelvic nodal irradiation is discussed with patients who have high-risk prostate cancer at our center, and the nodes are often treated. Clearly, having an accurate evaluation of the Gleason score is critical to making these decisions.

When the center opened in March 2013, we adopted the policy of the University of Washington Medical System and required that all patients with treated cancer have their tumor pathologic profile reviewed by members of the Department of Pathology at the University of Washington. For patients with prostate cancer, this essentially translated to an independent evaluation of the tumor Gleason score from the initial biopsy specimen. Since this is not a universal requirement of all proton centers, our center's administrative personnel were initially concerned that this review would cause inappropriate expense to the patient and could potentially delay unnecessarily the start of treatment. We agreed to evaluate the outcomes of our reviews after 1 year and, based upon the findings, decide whether to continue with the Gleason review process.

Patients and Methods

Patients with prostate cancer treated at the Seattle Cancer Care Alliance Proton Center during its first year of operation were identified through a review of center treatment records. These patients had been previously enrolled in a Proton Collaborative Group

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Table 1. Summary of Gleason score changes grouped according to value assigned at referral.

Initial Gleason score	Patient No.	Gleason score on review
3 + 3	19	3 + 3
	4	3 + 4
3 + 4	15	3 + 4
	3	3 + 3
4 + 3	5	4 + 3
	1	3 + 4
4 + 4	1	4 + 4
	2	4 + 3
4 + 5	2	4 + 5
	1	4 + 3

prospective registry (REG01-09) and had given permission for their medical records to be accessed for outcomes and research purposes. REG01-09 was opened at the center with the approval of the governing institutional review board, the Fred Hutchinson Cancer Center Institutional Review Board. Of the patients with prostate cancer treated between March 13, 2013, and April 14, 2014, a total of 53 were referred (or self-referred) from outside the University of Washington medical system, and their Gleason scores at the time of referral had been determined by outside pathologists. After evaluation to determine whether or not a patient was a potential candidate for proton therapy, center personnel obtained the biopsy specimens, which were reviewed by faculty at the Department of Pathology at the University of Washington who had expertise in prostate cancer. The results of this review were tabulated and analyzed. In the case of multiple cores with different Gleason scores, the highest score was used to characterize the tumor. This article only deals with Seattle Cancer Care Alliance Proton Center patients and is not an official Proton Collaborative Group publication.

Results

For 42 patients, the original Gleason score was confirmed on internal review. However, this left 11 patients for whom the Gleason score was changed. In 7 cases the original Gleason score was downgraded and in 4 cases the original Gleason score was upgraded. In all but 1 case, the Gleason score changed by only ± 1 unit; in the remaining case the Gleason score changed by -2 units. Analyzing the data according to the risk category assigned by the initial Gleason score, the greatest number of changes occurred for patients who were originally categorized as low risk with a Gleason score of 6 ($3 + 3$) and upon reclassification had their Gleason score changed to 7 ($3 + 4$). Four patients fell into this category. Among patients who were originally classified as intermediate risk via a Gleason score of 7, one was downgraded from ($4 + 3$) to ($3 + 4$), while 3 patients were reclassified as low risk by having a Gleason score of 7 ($3 + 4$) changed to a Gleason score of 6 ($3 + 3$). Three patients originally classified as having high-risk disease were reclassified as having intermediate-risk disease upon review. Two patients with initial scores of 8 ($4 + 4$) had a shift in score to ($4 + 3$). The greatest change occurred for a patient who was referred with a Gleason score of 9 ($4 + 5$) but whose Gleason score was shifted to 7 ($4 + 3$). **Table 1** summarizes this information and gives the absolute patient numbers in each category. The first entry in each row gives the number of patients in the category

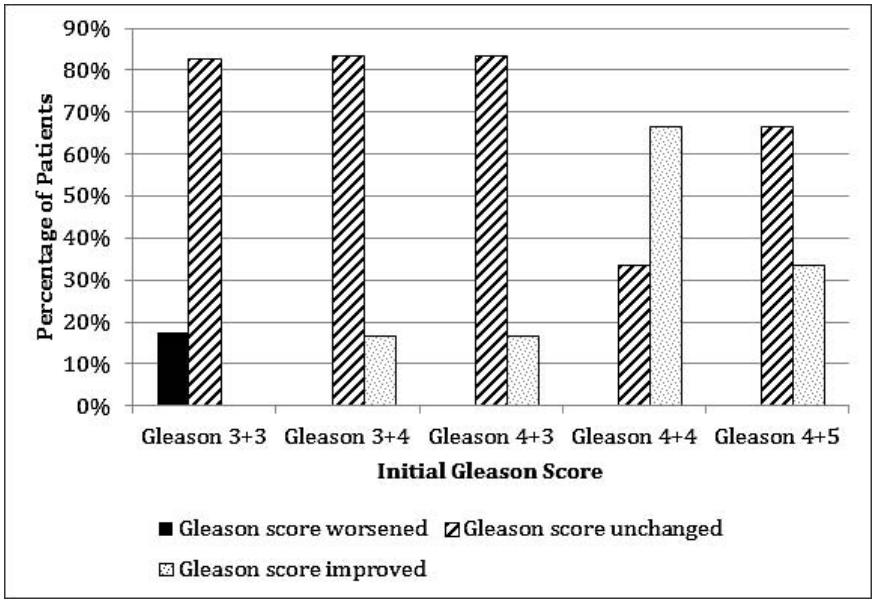

Figure 1. Percentage of Gleason score changes on review by University of Washington Medicine pathologists according to initial Gleason score.

whose Gleason scores were confirmed upon review. **Figure 1** displays the percentage of patients by initial Gleason score, whose new Gleason scores were either upgraded (worsened), downgraded (improved), or unchanged.

Discussion

During the first year of center operation, 11 of 53 (21%) patients with treated prostate cancer who were referred from outside of University of Washington Medicine had their Gleason scores modified on central review. This is a reflection of the large catchment area for such patients and the varying experience of the pathologist performing the initial Gleason determination. Gleason score is a key parameter in assigning a patient to a given risk category, which in turn is a major determinant of prognosis, and enters into guidelines for further evaluation and treatment recommendations. Hence, an accurate Gleason score is critical when comparing treatment outcomes to those of other proton centers and with other forms of treatment. There is a direct impact on patient care as well. At our own center the recommendation on whether to include the proximal seminal vesicles within the radiation field and whether to offer ADT in addition to radiation therapy hinges on whether a patient is "low risk" or "intermediate risk." The length of the recommended ADT varies between intermediate-risk and high-risk patients and pelvic nodal irradiation is offered only to patients in the high-risk category.

Similar Gleason reviews have been conducted for patients with prostate cancer treated at nonproton centers [16, 17]. Goodman et al [16] reviewed a total of 1905 slides relating to 268 biopsies and 120 prostatectomy specimens, using cases reported to the Metro Atlanta and Rural Georgia Surveillance Epidemiology and End Results registry between 2004 to 2005. For the biopsy specimens there was complete agreement in only 54% of cases, but like our own results, most disagreements involved only a 1-point change in the composite

Gleason score. Townsend et al [17] reviewed tissue specimens for 1649 men diagnosed with prostate cancer at an outside institution and then referred to the Fox Chase Cancer Center for treatment. They found a discordance rate of 26% for any change in the major or minor Gleason pattern. They also followed up on patient outcomes and determined that risk assessment according to the Fox Chase review correlated better with outcome than that determined by using the original Gleason score. They estimated that the treatment recommendation was changed for 9% to 26% of patients.

While there is a cost to the health care system associated with a pathology review of this type, the error rate that we noted at our own center is sufficiently high to warrant continuing this review. We feel that it would be important for other proton centers to sample their own data in this regard, particularly if they are entering patients with prostate cancer into prospective clinical trials or registries.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.
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