

Primary Gleason Pattern Does Not Affect Recurrence-Free Survival in Patients Receiving Radiotherapy for Prostate Cancer

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Abstract

Objective: To evaluate biochemical recurrence-free survival (b-RFS) in patients with Gleason score 7 prostate cancers treated with external beam radiotherapy at Ehime University Hospital.

Materials and Methods: Between January 2003 and October 2009, 63 patients with Gleason score 7 prostate cancers were treated with three-dimensional conformal radiotherapy (3D-CRT) at our institute. Of the 63 patients analyzed, 41 and 22 had a primary Gleason pattern of 3 and 4 carcinoma, respectively. Neoadjuvant hormonal therapy had been given to 37 patients (59%) for 6 months prior to radiotherapy. The American Society for Therapeutic Radiology and Oncology Phoenix consensus definition was used to determine the b-RFS after treatment.

Results: The overall b-RFS rate at 5 year was 71% and 77% for Gleason score 3+4 and 4+3 prostate cancer, respectively. The overall b-RFS at 5 year was 59% and 86% in Gleason score 3+4 patients with and without neoadjuvant hormonal therapy for 6 months, respectively.

Conclusions: Our results indicate that the 5 year b-RFS outcome with 3D-CRT is not dependent on Gleason score 3+4 versus 4+3 histological features, or on neoadjuvant hormonal therapy for 6 months in patients with a Gleason score of 3+4.

Keywords: Prostate cancer; Gleason score 7; Three-dimensional conformal radiotherapy

Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in Western countries. In Japanese men, morbidity and mortality rates of prostate cancer have increased [1]. Gleason score, the most widely accepted system for histologically grading prostate cancer, is a powerful predictor of disease progression and mortality [2]. Despite the established prognostic significance of the Gleason score in prostate cancer, Gleason score 7 cancer shows a heterogeneous clinical course. Gleason patterns 3 and 4 are included in various ratios in the cancers. Some investigations indicated that the primary Gleason pattern (the most prevalent pattern) is a predictor of disease progression in Gleason 7 cancer [3,4]. In fact, several studies have shown a significant difference in biological recurrence-free survival (b-RFS) following radical prostatectomy or brachytherapy in patients with Gleason score 7 prostate cancers [5-7]. However, the predominant effect of Gleason score (3+4 versus 4+3) upon results of external beam radiotherapy for Gleason score 7 prostate cancer is still imprecise [8]. In this study, we retrospectively reviewed the data from 63 patients who were diagnosed with Gleason score 7 prostate cancer and were treated with three-

dimensional conformal radiotherapy (3D-CRT) to clarify the prognostic significance of the primary Gleason pattern in this cohort of patients.

Patients and Methods

Between January 2003 and October 2009, 63 patients with Gleason score 7 prostate cancer were treated with 3D-CRT at Ehime University Hospital. All biopsy slides were reviewed by a single co-author (N.T.). All patients had pure Gleason 7 tumors without any tertiary Gleason pattern 5. The serum total prostate specific antigen (PSA) was measured by the ARCHITECT PSA assay (Abbott Japan Co. Ltd.).

The treatment was based on a CT scan (Eclipse, Varian Medical systems, CA, USA) performed with the patient in a supine position. Slice thickness was 5 mm. Patients were asked to have a comfortably full bladder and emptied bowels. The clinical target volume (CTV) was defined as the entire prostate and the base of the seminal vesicles. A total of 10 mm margins (anterior, posterior, and laterals) and 15 mm margins (cranial and caudal) were added to the total CTV to define the planning target volume (PTV). The iso-center was positioned in the center of the PTV and beams were shaped with multileaf collimators (Varian medical systems). A 10 MV linear accelerator was used to deliver radiation. The prescribed dose was 70 Gy in daily fraction of 2

Gy until April 2007, and the dose was increased to 72Gy thereafter. Elective pelvic lymph nodes irradiation was not performed.

Patients were followed by checking serum PSA levels every 2-3 months for 3 years and 4-6 months thereafter. Other examinations were performed if clinically indicated. Biochemical failure was defined as a PSA level >2 ng/ml greater than the PSA nadir according to the American Society for Therapeutic Radiology and Oncology Phoenix Consensus definition. The b-RFS rates were estimated using the Kaplan-Meier method.

Results

The patient characteristics are listed in Table 1. The median age at the start of radiotherapy was 73 years (range, 58-83 years). Gleason score 3+4 tumor was identified in 41 of 63 patients, with those remaining having Gleason score 4+3 tumors. The median pre-treatment serum PSA level was 10.5 ng/ml (range 3.3-107.8 ng/ml). There was no statistically significant difference in age, pre-treatment PSA, and clinical stage between the 2 groups. Neoadjuvant hormonal therapy had been given to 37 patients for 6 months prior to radiotherapy, 17 with a Gleason score of 3+4 and 20 with a Gleason score of 4+3. Hormonal therapy consisted of luteinizing hormone-releasing hormone analogue alone in 19 patients, antiandrogen alone in 1 patient and LH-RH analogue plus antiandrogen in 17 patients. Seventeen (41%) out of 41 patients with Gleason score 3+4 and 20 (91%) out of 22 patients with Gleason score 4+3 had received neoadjuvant hormonal therapy for 6 months.

Variable	Gleason 3+4 (n=41)	Gleason 4+3 (n=22)	p-Value
Clinical Characteristics			
Age(Years)	71	74	0.39
Pre-treatment PSA (ng/ml)	9.78	13.5	0.08
Clinical stage			
T1cT2	30	16	0.74
T3	11	6	
Androgen deprivation therapy	17 (41%)	20 (91%)	<0.01

Table 1: Clinical characteristics of patients treated with external beam radiotherapy.

Median follow-up of all patients was 48 months (range 28-108 months). Ten patients (6 for Gleason score 3+4 and 4 for 4+3) experienced biochemical recurrence and 6 patients (5 for Gleason score 3+4 and 1 for 4+3) died from causes unrelated to treatment. The overall b-RFS rate at 5 year was 71% and 77% in patients with Gleason score 3+4 and 4+3, respectively (Figure 1). No statistically significant difference was identified between the 2 groups ($p=0.94$).

Figure 2 illustrates the biochemical outcome for Gleason 3+4 patients treated with ($n=17$) or without ($n=24$) neoadjuvant hormonal therapy for 6 months prior to 3D-CRT. The overall b-RFS at 5 year was 59% and 86% in patients with and without neoadjuvant hormonal therapy, respectively ($p=0.14$).

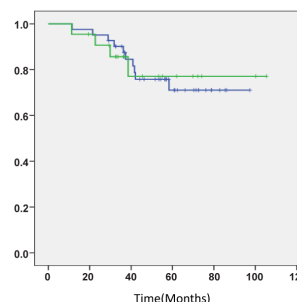


Figure 1: b-RFS stratified by primary Gleason pattern. N=63, 41 and 22 patients had Gleason score 3+4 (blue) and 4+3 (green), respectively.

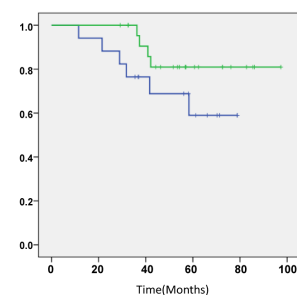


Figure 2: b-RFS with or without neoadjuvant hormonal therapy in patients with a Gleason score of 3+4. N=41, 17 and 24 patients received 3D-CRT with (blue) and without (green) neoadjuvant hormonal therapy, respectively.

Discussion

In the present study, Gleason score 7 prostate cancer patients treated with 3D-CRT showed a favorable b-RFS, and there were no significant differences between the patients with a Gleason score pattern of 3+4 or 4+3. A previous study using radical prostatectomy specimens determined that Gleason pattern of 4+3 prostate cancer independently predicted more advanced disease at surgery [9]. In addition, several published studies have investigated the prognostic value of the primary Gleason pattern in the clinical setting. They confirmed that in terms of b-RFS and the need for salvage therapy, a primary Gleason pattern of 4 seemed to be associated with a worse prognosis than that of 3 [5,10]. On the other hand, there have been conflicting results. Merrick et al. reported no statistically significant difference in b-RFS outcome when results were stratified by the dominant pattern in Gleason score 7 histological features (89% for 3+4 versus 92% for 4+3, $p=0.700$) [11]. In addition, they reported that the primary Gleason pattern did not affect survival outcome in Gleason score 7 prostate cancer patients [12]. Another report has also indicated that there was no significant difference in 5 year b-RFS between the 2 groups (97% for 3+4 88% for 4+3 versus) [13]. Recently, in patients treated permanent prostate brachytherapy, Uesugi et al. indicated that a primary Gleason pattern of 4 resulted in a poorer b-RFS than that of

pattern 3 [7]. For Gleason score 7 prostate cancer patients receiving 3D-CRT, the effect of the primary Gleason pattern on survival outcome is still unclear. Only a nonstatistical trend for improved outcome has been reported for Gleason score 3+4 versus 4+3 (5 year b-RFS rate; 89% versus 92%, $p=0.700$) [8]. It is possible that radiotherapy such as 3D-CRT and brachytherapy may negate the impact of the primary Gleason pattern.

Primary radical therapeutic options for localized prostate cancer include radical prostatectomy, external beam radiotherapy, and brachytherapy. The selection of primary intervention is decided based on clinical factors obtained before treatment. Risk stratification of localized prostate cancer is well established. Gleason score 7 is included as one of the factors of intermediate risk group in National Comprehensive Cancer Network (NCCN) Guidelines [14]. The guidelines for patients undergoing external beam radiotherapy recommend 3D-CRT/IMRT with daily image-guided radiation therapy +/- and short-term (4-6 months) neoadjuvant/concomitant/adjuvant hormonal therapy. In our series, hormonal therapy for 6 months in a neoadjuvant setting was administered in 17 patients (41%) with a Gleason score of 3+4 prostate cancer. To assess whether neoadjuvant hormonal therapy for 6 months is needed for all patients with this Gleason score, we compared b-RFS between the patients with or without prior hormonal therapy. The addition of neoadjuvant hormonal therapy for 6 months prior to 3D-CRT did not affect the outcome of patients with Gleason 3+4 prostate cancer. Our present result may suggest that patients with Gleason score 3+4 prostate cancer can be appropriately managed by 3D-CRT alone. Nowadays, the use of high-dose radiation therapy is commonplace and it is likely that the use of prior hormonal therapy will be reduced in the future. More detailed study is required to assess the potential usefulness of short-term neoadjuvant hormonal therapy for patients with Gleason 3+4 prostate cancer.

Limitations of the current study include the retrospective, single-institutional nature of the evaluation, the limited number of patients, and a relatively short follow-up period at the time of analysis. The most critical problem is that reliance on biopsy findings rather than whole section prostate specimens. However, in the case of radiotherapy, Gleason scores can only be judged from biopsy specimens. Amin et al. reported that 26% of the cases with a Gleason score of 3+4 on biopsy were upgraded to 4+3 or higher at radical prostatectomy and 40% of the cases with a Gleason score of 4+3 on biopsy were downgraded to 3+4 or lower [15]. This cross-contamination complicates the stratification of outcomes in the patients with Gleason score 7 prostate cancer. The discovery of additional molecular or pathological markers may help to further stratify patients with a biopsy diagnosis of Gleason score 7 prostate cancer into more accurate prognostic groups.

In conclusion, these results suggest that the 5 year b-RFS outcome following 3D-CRT is not dependent on Gleason score 3+4 versus 4+3 histological features. In addition, neoadjuvant hormonal therapy for 6 months did not affect the outcome of Gleason 3+4 prostate cancer patients. To improve the ability of clinicians to counsel patients after treatment with 3D-CRT, other markers recognizing the distinction in Gleason 7 prostate cancer are needed.

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