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ORIGINAL ARTICLE

Outcomes of T3a Prostate Cancer with Unfavorable Prognostic Factors Treated with Brachytherapy Combined with External Radiotherapy and Hormone Therapy

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Key words: T3a; prostatic neoplasms; unfavorable; trimodality therapy

Objective To evaluate the outcomes of T3a prostate cancer with unfavorable prognostic factors treated with permanent interstitial brachytherapy combined with external radiotherapy and hormone therapy.

Methods From January 2003 to December 2008, 38 patients classified as T3a prostate cancer with unfavorable prognostic factors were treated with trimodality therapy (brachytherapy + external radiotherapy + hormone therapy). The prescription dose of brachytherapy and external radiotherapy were 110 Gy and 45 Gy, respectively. The duration of hormone therapy was 2-3 years. The endpoints of this study included biochemical failure-free survival (BFFS), distant metastasis-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS). Survival curves were calculated using the Kaplan-Meier method. The Log-rank test was used to identify the prognostic predictors for univariate analysis.

Results The median follow-up was 71 months. The serum pre-treatment prostate-specific antigen (PSA) level ranged from 10.0 to 99.8 ng/ml (mean 56.3 ng/ml), the Gleason score ranged from 5 to 9 (median 8), and the percentage of positive biopsy cores ranged from 10% to 100% (mean 65%). The 5-year BFFS, DMFS, CSS, and OS rates were 44%, 69%, 82%, and 76%, respectively. All biochemical failures occurred within 40 months. The percentage of positive biopsy cores was significantly correlated with BFFS, DMFS, and OS (all $P=0.000$), and the Gleason score with DMFS ($P=0.000$) and OS ($P=0.001$).

Conclusions T3a prostate cancer with unfavorable prognostic factors presents not so optimistic outcome. Hormone therapy should be applied to prolong the biochemical progression-free or metastasis-free survival. The percentage of positive biopsy cores and the Gleason score are significant prognostic factors.

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PROSTATE cancer is the second most common malignant tumour in men world-wide and is the leading cause of death in economically developed countries.¹ The incidence of prostate cancer in Eastern Asia, such as China, is not as high as it is in Europe and Northern America,² which may be mainly explained by difference in races and lifestyle habits. However, due to the aging of the population and the introduction of prostate-specific antigen (PSA) screening, there has been a rapid increase in the detection of prostate cancer in Chinese people in recent years. However, T3a prostate cancer is less common compared to other stages of Pca.³

According to the guidelines of The European Association of Urology (EAU), T3a prostate cancer is defined as extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement. Classified as locally advanced prostate cancer, T3a stage disease is usually associated with a high risk of biochemical failure and distant metastasis. The optimum treatment strategy for T3a prostate cancer remains controversial.⁴ Generally, monotherapy, such as brachytherapy, external radiotherapy or radical prostatectomy, often lead to poor prognosis.⁵⁻⁷ In recent decades, combined treatment has revealed promising local tumor control and reasonable long-term outcomes.⁸⁻¹¹ For T3a prostate cancer specifically, trimodality therapy is an appropriate option.¹²

The National Comprehensive Cancer Network (NCCN) Guidelines defines prostate cancer with multiple high-risk factors (PSA >20 ng/ml, Gleason score 8 to 10, or clinical T-stage T3 to T4) as a very high-risk prostate cancer (VHRPC).¹³ In this article, we enrolled a series of T3a stage patients with markedly elevated PSA levels, high Gleason scores or a high percentage of positive biopsy cores (>50%), most of which met all three criteria. We present the initial experience regarding the treatment of this cohort with a combination of permanent interstitial brachytherapy, external radiotherapy and hormone therapy. The clinical outcomes included biochemical failure-free survival (BFFS), distant metastasis-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS). In addition, we also investigated the predictive factors for BFFS, DMFS and OS.

PATIENTS AND METHODS

Patient selection

From January 2003 to December 2008, a total of 38 patients with markedly elevated PSA levels, high Gleason scores or a high percentage of positive biopsy cores (>50%)

were assessed as T3a stage prostate cancer based on digital rectal examination and magnetic resonance imaging (MRI). No patient had the evidence of distant metastasis on contrast-enhanced computed tomography (CT) and bone scan.

Treatment

All the patients were treated with a combination of permanent interstitial brachytherapy, external radiotherapy, and hormone therapy. For brachytherapy, we adopted the Seattle technique for the entire treatment course.¹⁴ A preplanning transrectal ultrasound volume study was performed in each patient. The target volume consisted of the prostate gland with a 5-mm periprostatic margin. The intraoperative procedure for ¹²⁵I seed implantation involved the use of a transperineal approach under transrectal ultrasound and template guidance. The patients were placed in the lithotomy position under spinal or general anaesthesia. A needle guidance template was attached close to the perineum and needles were inserted under real-time transrectal ultrasound monitoring. Fluoroscopy, combined with transrectal ultrasound, was used to monitor needle depth and seed deposition. The prescription dose was 110 Gy. A pelvic X-ray was carried out for the preliminary analysis of the distribution of seeds 6-8 hours after the implantation. A CT scan was required to evaluate the D90 (the minimum percentage of the prescription dose that covers the planning target volume).

Of all the selected patients, 13 received external radiotherapy 1-2 months before brachytherapy and the rest received external radiotherapy 2-4 months after brachytherapy. An intensity-modulated technique was used to deliver the external radiotherapy. The planning target volume contained the prostate, seminal vesicles, and pelvic lymph nodes. The prescription dose was 45 Gy, and the treatment was delivered in daily fractions of 1.8-2.0 Gy, 5 days per week.

Hormone therapy was administered continuously before or after brachytherapy. The treatment protocol was maximum androgen blockade, which consisted of a luteinising hormone-releasing hormone agonist in conjunction with an antiandrogen (bicalutamide 50 mg daily). The treatment duration was 2-3 years.

Follow-up

All the patients were monitored using the digital rectal examination, serum PSA and testosterone measurement monthly for the first 3 months, then every 3 months over the rest of the first two years, every 6 months thereafter. If tumour progression was detected, the interval of follow-up

was shortened. When necessary, the abdominal and pelvic CT and bone scan were required to seek the evidence of distant metastasis. The endpoints of this analysis included BFFS, DMFS, CSS, and OS. According to the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria,¹⁵ the definition of biochemical failure was: an increase of 2 ng/ml after the nadir had been reached. Distant metastasis was defined as CT or bone scan evidence of disease outside the pelvis. Deaths in the setting of metastatic disease were classified as prostate cancer-specific death.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences, version 19.0 (SPSS, Chicago, IL, USA) software. Data were expressed as means $\pm$ SD (range). Survival curves were calculated using the Kaplan-Meier method. Log-rank test was used to identify the prognostic predictors for univariate analysis. Multivariate analysis could not be conducted due to the small sample size. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 71.0 $\pm$ 7.3 years (range 48-81 years) and the mean pre-treatment PSA was 56.3 $\pm$ 23.8 ng/ml (range 10.0-99.8 ng/ml). The Gleason score varied from 5 to 9, with 20 patients (53%) having a Gleason score $\geq$ 8. The mean percentage of positive biopsy cores was 65.0% $\pm$ 27.3% (range 10%-100%). The mean D90 of brachytherapy was 108.0 $\pm$ 5.4 Gy (range 96-115 Gy) and the prescription dose of external radiotherapy was 45 Gy. The duration of hormone therapy was 2-3 years.

With a median follow-up of 71 months, the 5-year BFFS, DMFS, CSS, and OS rates for the entire cohort were 44%, 69%, 82%, and 76%, respectively, and 19 patients experienced biochemical failure. The mean biochemical failure time was 13.4 $\pm$ 12.5 months (range 1-40 months); 13 patients developed distant metastatic prostate cancer at an average of 19.7 $\pm$ 25.1 months (range 1-70 months) after brachytherapy. Of all the patients, 9 died of prostate cancer, while 6 passed away due to other causes, with an average of 52.2 $\pm$ 30.9 months (range 9.0-98.5 months) after brachytherapy. The survival curves of BFFS, DMFS, CSS, and OS are shown in Figure 1.

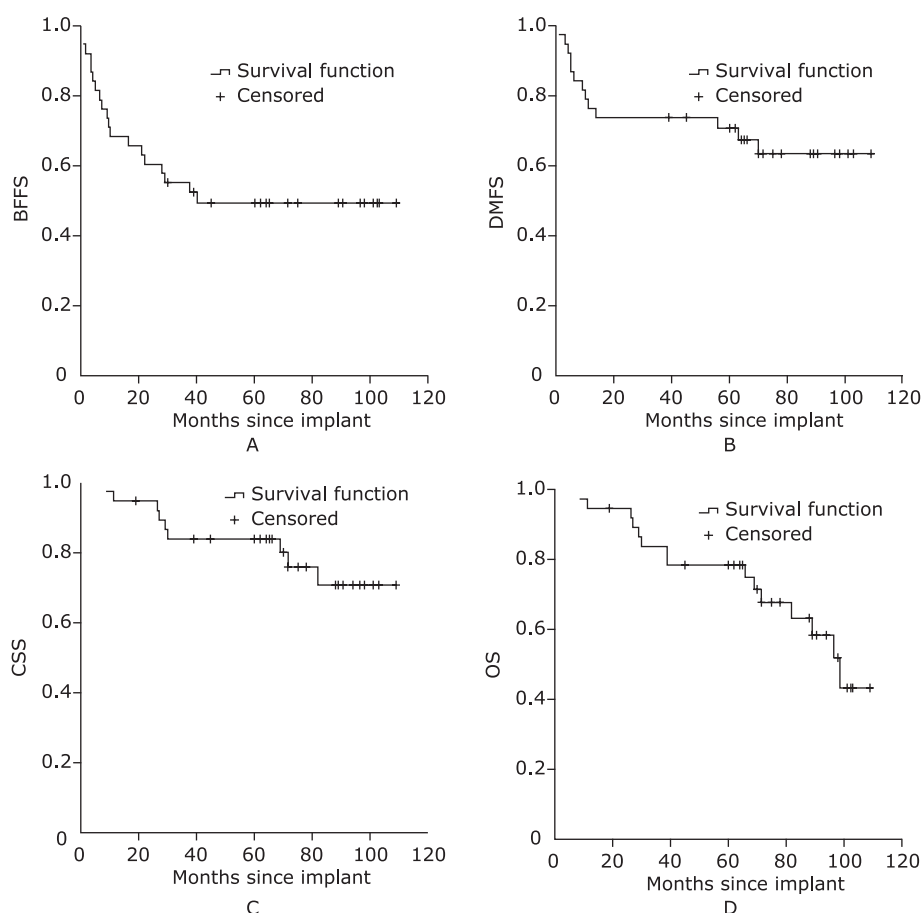


Figure 1. Survival curves of biochemical failure-free survival (BFFS, A), distant metastasis-free survival (DMFS, B), cancer-specific survival (CSS, C), and overall survival (OS, D).

The predictive factors used for the univariate regression analysis were age, prostate volume, serum pre-treatment PSA, Gleason score, and percentage of positive biopsy cores. The univariate analysis revealed that the percentage of positive biopsy cores was significantly corre-

lated with BFFS ($P = 0.000$), DMFS ($P = 0.000$), and OS ($P = 0.000$) (Fig. 2); the Gleason score was significantly correlated with DMFS ($P = 0.000$) and OS ($P = 0.001$) (Fig. 3); and patients' age was significantly correlated with OS ($P = 0.023$) (Fig. 4).

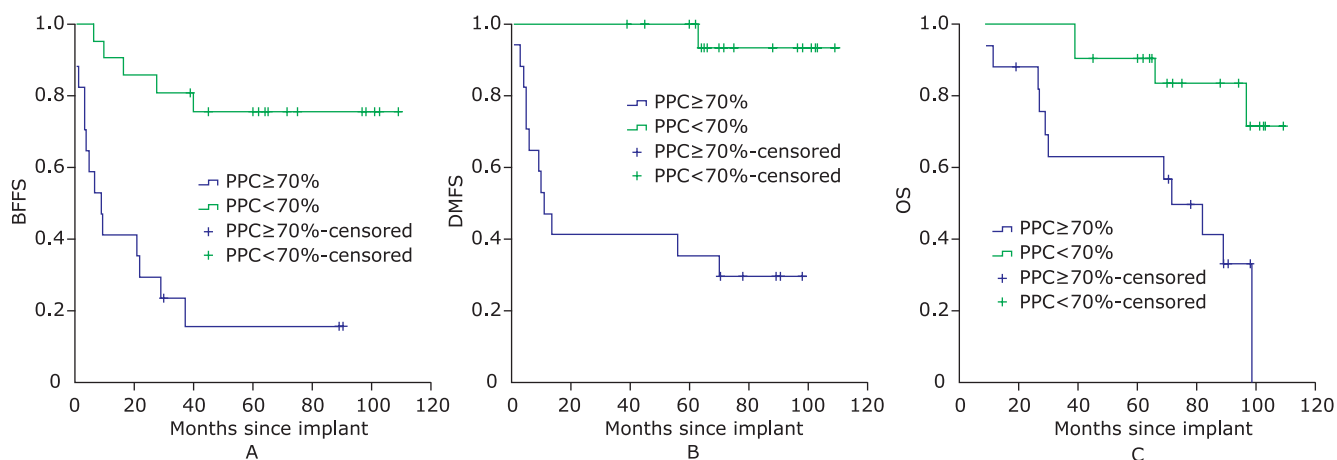


Figure 2. Univariate analysis revealed that the percentage of positive biopsy cores (PPC) was significantly correlated with BFFS (A), DMFS (B), and OS (C).

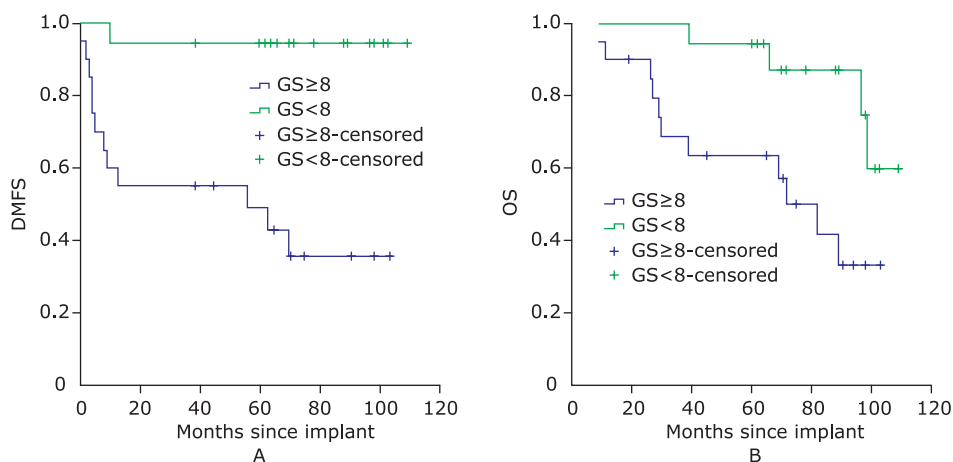


Figure 3. Univariate analysis revealed the Gleason score (GS) was significantly correlated with DMFS (A) and OS (B).

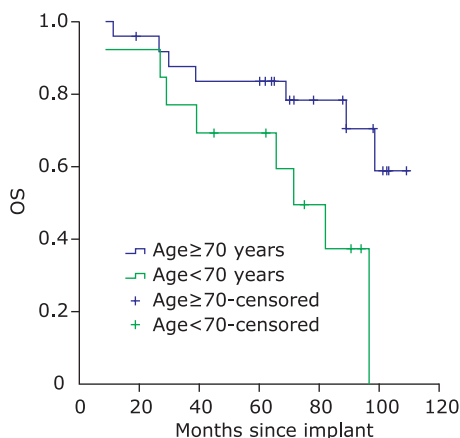


Figure 4. Univariate analysis revealed patients' age was significantly correlated with OS.

DISCUSSION

Because of the widespread implementation of PSA screening, T3a or higher clinical stage prostate cancer is not common today.^{3, 16} Consensus on the clinical management of T3a stage prostate cancer, which is classified as a high-risk or locally advanced prostate cancer, has been difficult to achieve. Usually, T3a disease along with markedly elevated PSA level or high Gleason score is defined as VHRPC (PSA >20 ng/ml, Gleason score 8 to 10, or clinical T-stage T3 to T4). These groups of patients often exhibit a high risk of biochemical failure and distant metastases, particularly micro-metastases are often present at the initial diagnosis even when there is no evidence of distant metastasis on the CT or bone scan. The treatment goals are to potentially prolong biochemical progression-free or metastasis-free survival, and to improve quality of life.

In general, radiotherapy or radical prostatectomy as monotherapy has often produced limited long-term success. In a prospective randomised trial, Bolla *et al*⁵ investigated the long-term results in 193 patients with locally advanced prostate cancer, who were assigned to radiotherapy alone. The external radiotherapy protocol was 50 Gy radiations to the pelvis over 5 weeks, and 20 Gy over 2 weeks as a prostatic boost. The 5-year clinical disease-free survival and OS were 40% and 62%, respectively. van den Ouden *et al*⁶ enrolled T3 prostate cancer patients treated with radical prostatectomy without adjuvant treatment. The mean preoperative PSA was 20.5 ng/ml. The 5-year biochemical progression, clinical progression, CSS, and OS were 71%, 41%, 85%, and 75%, respectively. Furthermore, brachytherapy without additional treatments also leads to poor results. Lee *et al*⁷ reported that the 5-year BFFS was 54% for intermediate- to high-risk (including T3a stage) prostate cancer patients treated with permanent radioactive seed implantation alone.

Although the optimum treatment strategy for T3a prostate cancer remains controversial, combined treatment is usually recommended. Given that micro-metastases are often present when this condition is first diagnosed, the use of concomitant or adjuvant hormone therapy is often required. Hormone therapy can reduce the risk of distant metastases by potentially sterilising the micro-metastases that are already present at the time of diagnosis based on cytoreductive and synergistic qualities. In Lee *et al*'s⁷ retrospective review, hormone therapy significantly improved the 5-year actuarial BFFS in intermediate- to

high-risk prostate cancer patients treated with brachytherapy (79% vs. 54%). The RTOG 85-31 study recruited 977 patients with clinical stage T3 or those with regional lymphatic involvement for the treatment of either radiotherapy plus adjuvant goserelin or radiotherapy alone. The 10-year outcomes showed that androgen suppression as an adjuvant was associated not only with a reduction in disease progression but with a statistically significant improvement in absolute survival.¹⁷

In recent years, there has been an increasing number of articles reporting the long-term results of T3a prostate cancer patients treated with trimodality therapy (permanent interstitial brachytherapy combined with external radiotherapy and hormone therapy). In most studies, pre-treatment prognostic factors significantly influenced the outcomes. T3a stage with relatively favourable prognostic factors often indicates promising tumour control and long-term endpoints. In contrast, if the prognostic features include multiple unfavourable elements, such as high-grade disease or markedly elevated PSA level, less optimistic results may be obtained. Pistis *et al*¹⁸ reported encouraging preliminary biochemical control after radiation therapy combined with brachytherapy as a boost for locally advanced prostate cancer (T3a accounted for 49.1%). Most of the patients underwent long-term hormone therapy. The mean pre-treatment PSA level was 19.5 ng/ml and the proportion of patients with Gleason score ≥ 8 was 28.1%. The 4-year BFFS rate was 97.4%. Similarly, Hsu *et al*¹⁹ reported a retrospective analysis of combined modality treatment for locally advanced prostate cancer. The median pre-treatment PSA was 8.2 ng/ml and T3 accounted for 44% of the included patients. And 23% had a Gleason score ≥ 8 . The 4-year estimates of OS and disease-free survival were 98% and 92%, respectively. However, treatment is less tolerated in patients with higher disease stage. Carpenter *et al*²⁰ assigned trimodality therapy for 97 patients with extraprostatic prostate cancer. Trends toward worse outcomes were noted with increasing Gleason score, with 7-year BFFS rates being 86%, 71%, and 55% for scores of 6 or less, 7, and 8-10, respectively. Shilkrut *et al*²¹ conducted a retrospective review on combined modality treatment in patients with VHRPC (those with at least 2 of the high-risk factors: PSA >20 ng/ml, Gleason score 8 to 10, or clinical T3 to T4 stage). The median PSA of the included patients was 30.7 ng/ml. T3a or higher clinical stage and Gleason score ≥ 8 accounted for 55% and 84% of the entire cohort, respectively. BFFS, DMFS, and CSS for all the patients at 8 years were 50.6%, 68.5%, and 78.7%, respectively.

In this study, for the whole cohort, the mean pre-treatment PSA was 56.3 ± 23.8 ng/ml, 53% of the patients

had a Gleason score of 8 or higher and the mean percentage of positive biopsy cores was $65.0\% \pm 27.3\%$. With a median follow-up of 71 months, the 5-year BFFS, DMFS, CSS, and OS rates were 44%, 69%, 82%, and 76%, respectively. The less than satisfactory results on one hand can be explained by the multiple unfavourable pre-treatment prognostic factors. On the other hand, the results revealed the necessity of applying combined treatment, including permanent interstitial brachytherapy, external radiotherapy and hormone therapy in T3a patients with these characteristics, as verified by the report of Shilkrut *et al.*²¹ Furthermore, in the present study, all the biochemical failures occurred within 40 months, and 63% of them further developed distant metastatic prostate cancer. As hormone therapy alone for prostate cancer treatment would inevitably lead to biochemical failure in 12-33 months,²² we assumed that micro-metastases may exist in this group of patients even though there was no evidence of distant metastases based on various examinations when they were diagnosed. This directly further confirms the role of hormone therapy in T3a stage prostate cancer with unfavourable prognostic factors.

Different reports have identified different significant prognostic factors. Nickers *et al.*⁹ showed that a higher Gleason score or T stage or pre-treatment PSA value were significantly correlated with lower biochemical no evidence of disease but androgen deprivation therapy was not, based on the univariate analysis; the pre-treatment PSA value shifted to borderline significance in the multivariate analysis. Ishiyama *et al.*²³ analysed the stage, Gleason score, PSA level, NCCN criteria and age to determine the predictive factors. In univariate analysis, clinical T stage, Gleason score and NCCN risk-group were detected as predictive factors for biochemical non-evidence of disease. Based on the multivariate analysis, no risk factor reached the level of statistical significance. Galalae *et al.*²⁴ reported that the risk group, stage, initial PSA, and Gleason score were the predictive factors for biochemical control; whereas age, follow-up interval and androgen deprivation therapy were not. In contrast, Pellizzon *et al.*¹⁰ showed that pre-treatment PSA value, together with Gleason score and T stage were not significant predictors of biochemical no evidence of disease. According to the data of this study, among age, percentage of positive biopsy cores, prostate volume, pre-treatment serum PSA, and Gleason score, the percentage of positive biopsy cores and Gleason score were the significant prognostic factors in the univariate analyses. Limited to small sample size, multivariate analysis can not be expressed. We suppose that patient baseline characteristics and the size of the study sample can partly

account for these findings.

In conclusion, T3a prostate cancer with high-grade disease, markedly elevated PSA level or high volume of disease based on needle biopsy is associated with not so optimistic outcome even after treated with trimodality therapy. To prolong the biochemical progression-free or metastasis-free survival, hormone therapy is essential for this series of patients. In univariate regression analysis, the percentage of positive biopsy cores and Gleason score were verified as the significant prognostic factors for BFFS, DMFS, and OS. Randomised studies with a larger sample are required to verify these findings.

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