

Prostate cancer with nodular bladder invasion (stage T4N1) cured by low-dose-rate brachytherapy with seminal vesicle implantation in combination with external beam radiotherapy of biologically effective dose ≥ 220 Gy: a case report

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Abstract

Purpose: Prostate cancer with nodular bladder invasion (stage T4 prostate cancer) is an extremely difficult clinical entity to achieve complete cure. So far, there has been no clear report demonstrating complete cure of prostate cancer with nodular bladder invasion, stage T4 prostate cancer.

Case presentation: In this case report, the author presents a 55-year-old man with a diagnosis of advanced prostate cancer invading into the bladder wall with pelvic lymph node metastasis (T4N1M0 disease). The patient was treated with biologically effective dose (BED) ≥ 220 Gy of high-dose radiotherapy, using low-dose-rate (LDR) brachytherapy in combination with whole pelvis (WP) external beam radiotherapy (EBRT) and short-term androgen deprivation therapy (ADT): neo-adjuvant six months plus adjuvant six months ADT. There was no grade 2 genitourinary (GU) and gastrointestinal (GI) toxicity during follow-up. There was no evidence of hematuria, nor rectal bleeding in the follow-up. The patient stays healthy without biochemical failure and without bowel and urinary troubles at six years.

Conclusions: Along with previous outstanding data of BED ≥ 220 Gy LDR-based radiotherapy for high-risk and very high-risk prostate cancer patients, including pelvic lymph node metastasis, the present report, in which the patient was treated with BED ≥ 220 Gy of high-dose radiotherapy, LDR brachytherapy in combination with WP EBRT may be an optimal treatment for prostate cancer with nodular bladder invasion with lymph node metastasis (T4N1 disease).

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Key words: prostate cancer with bladder invasion, T4 prostate cancer.

Purpose

Prostate cancer with bladder invasion, stage T4 prostate cancer, is an extremely difficult clinical entity to achieve a complete cure. So far, there has been no clear report on complete cure of prostate cancer with bladder invasion, stage T4 prostate cancer.

We have previously shown outstanding clinical outcomes by dose escalation for high-risk and very high-risk prostate cancer with regional lymph node metastasis: biochemical failure-free survival (BFFS) rate of 95.2% at 5 years by low-dose-rate (LDR) in combination with external beam radiotherapy (EBRT) of biologically effective dose (BED) ≥ 220 Gy [1]. Since no clear report on complete cure of prostate cancer with nodular bladder invasion (stage T4 prostate cancer) is available, this present case report may highlight the effectiveness of BED ≥ 220 Gy

of high-dose radiotherapy, using LDR brachytherapy in combination with whole pelvis (WP) EBRT with short-term androgen deprivation therapy (ADT) for T4 prostate cancer. The key for successful outcome for such a difficult case is BED and LDR seed implantation technique. The author explains this technique in detail.

Case report

In a regional hospital, a 55-year-old man was diagnosed with a Gleason 4 + 4 prostate cancer, clinical stage T4. The prostate specific antigen (PSA) before the prostate biopsy was 37 ng/ml. The patient sought the author's medical advice and treatment. Then, he visited the author's specialized outpatient clinic for prostate brachytherapy in 2013. Upon the first interview, the patient complained of severe urinary frequency and difficulty in urination.

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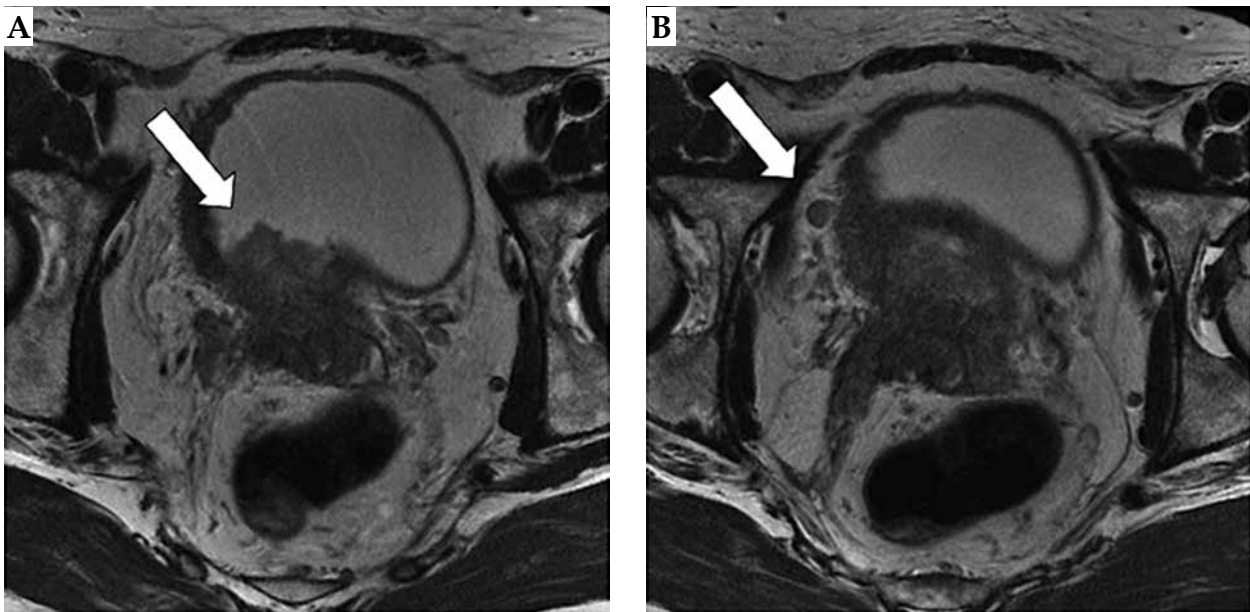


Fig. 1. Axial T2-weighted magnetic resonance images of the prostate. **A)** A large prostate tumor with hypo-intensity extended into the right bladder wall. The white arrow indicates the invasion of prostate cancer into the bladder. **B)** Bilateral seminal vesicles invasion. A lymphadenopathy is also observed in the right obturator lesion suggesting pelvic node lymph node metastasis (white arrow)

Digital rectal examination showed a hard nodule on the prostate. Nine trans-rectal biopsy specimens obtained from the regional hospital all showed Gleason 4 + 4. Magnetic resonance imaging (MRI) revealed clinical T4 stage, with bladder invasion and bilateral seminal vesicles (SV) invasion (Figure 1). Consistent with the MRI results, the cystoscopic findings showed nodular bladder invasion in the right trigone, near the bladder neck (Figure 2), and lymph node metastasis in the right obturator lesion (Figure 1). After neo-adjuvant ADT of six months, the patient received LDR brachytherapy with seminal vesicles implantation. LDR seeds implantation was conducted with iodine-125 (¹²⁵I) seeds using real-time ultrasound-guided technique. Radioactive seeds were implanted into the prostate using a Mick applicator (Mick Radio-Nuclear

Instruments, Inc., Mount Vernon, NY, USA). The seeds were implanted, and the dosimetry plan was updated before further procedures, so that the plan could evolve dynamically as seeds were implanted. Planning was performed with VariSeed 8.0 planning system (Varian Medical Systems, CA, USA).

Seed activity used during implantation was 0.284 mCi. Seventy-five seeds (OncoSeed; Nihon Medi-Physics Co. Ltd., Tokyo, Japan), including ten seeds for seminal vesicles were implanted (Figure 3). We routinely conduct seed implantation to the seminal vesicle for T3b cases [1].

The method of seminal vesicle implantation is described elsewhere [2]. Post-implant dosimetry with computer tomography (CT) and MRI guidance was carried out at one month after the implantation. Dosimetry at one

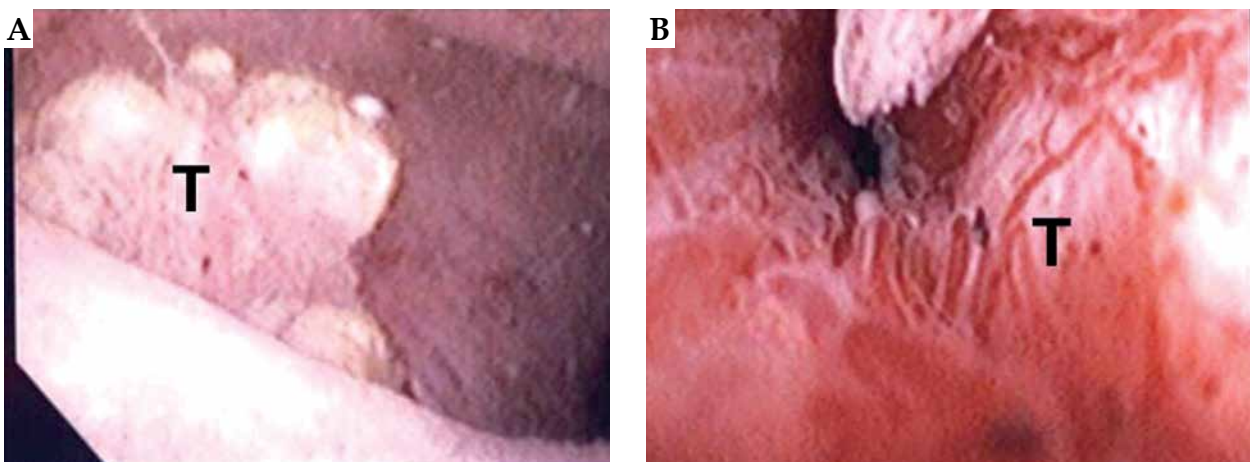


Fig. 2. Cystoscopy findings of the nodular bladder invasion of prostate tumor. **A)** An irregular surface of solid and nodular tumor is located in the right trigone, near the bladder neck. T - nodular bladder invasion of the prostate tumor. **B)** The neck of the tumor shows hyper vascular appearance. T - neck of the nodular bladder invasion of prostate tumor

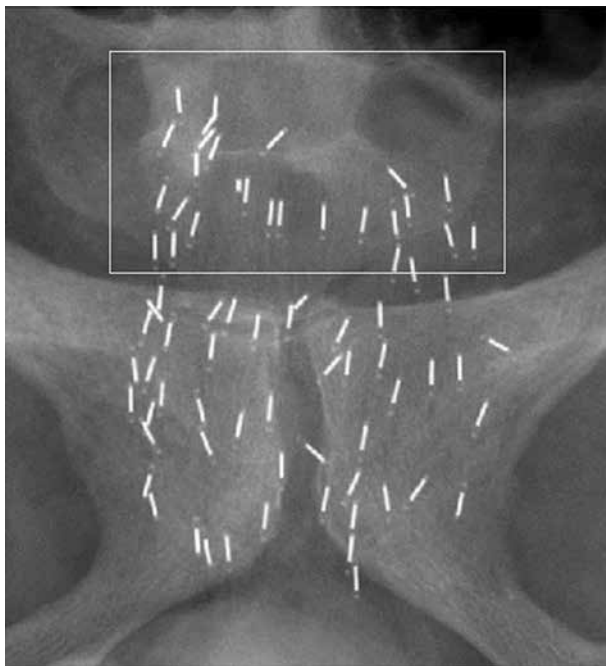


Fig. 3. Plain X-ray image of the seed implantation. A total of 75 seeds were implanted. The seeds in the white box indicates seeds implanted to the seminal vesicles and the prostate protruding into the bladder

month after the seed implantation is shown in Table 1. In order to compare and estimate radiation doses between LDR and EBRT, already established BED equations were used [3,4,5]: $BED \text{ for EBRT} = nd [1 + (d/\alpha/\beta)]$, where n - number of fractions, d - dose per fraction, and α/β - a tissue- and effect-specific parameter associated with the linear-quadratic model. The equation used to calculate BED for LDR permanent decaying implants with ^{125}I BED for LDR $= (R0/\lambda) \{1 + [R0/(\mu + \lambda) (\alpha/\beta)]\} = D_{90} [1 + D_{90} \times (\ln2/T_{1/2}) \times (\ln2/t_{1/2} + \ln2/T_{1/2}) - 1 \times (\alpha/\beta) - 1]$, where $R0$ - initial dose rate of implant $= (D_{90}) (\lambda)$, λ - radioactivity decay constant $= 0.693/T_{1/2}$, $T_{1/2}$ - radioactive half-life of isotope, μ - repair rate constant $= 0.693/t_{1/2}$, and $t_{1/2}$ - tissue repair halftime. The equation used to calculate BED for LDR permanent decaying implants with ^{125}I BED for $t_{1/2}$ - tissue repair halftime [3,4,5]. The values used for these constants for prostate carcinoma were $\alpha/\beta = 2 \text{ Gy}$, $t_{1/2} = 1 \text{ h}$, $T_{1/2} = 60 \text{ days}$ for ^{125}I . By convention, the unit of BED calculated when $\alpha/\beta = 2 \text{ Gy}$ is Gy_2 . The BED values for treatments including both implant and EBRT were calculated by adding the BED computed for each treatment [3]. Further information regarding BED calculations and the rationale for selection of α/β ratio of 2 Gy for prostate cancer have been previously described in detail [4].

To achieve a BED of 220 Gy, D_{90} of 130 Gy have to be delivered (post-implant D_{90}) by using ^{125}I seed implantation in combination with 45 Gy EBRT in 1.8 Gy fraction [6]. In order to secure 130 Gy of D_{90} at post- ^{125}I seed implantation, we usually set D_{90} at implantation from 135 Gy to 145 Gy [1].

By complying with the above-mentioned implantation policy, clinical target volume (CTV) was covered with 130 Gy and CTV with margin was covered with 110 Gy

Table 1. Dosimetric parameters at one month after ^{125}I seed implantation in the present case

Parameter	
Prostate D_{90} (Gy)	130
V_{150} (%)	46.5
V_{100} (%)	96.8
UD_{30} (Gy)	150.7
R_{100} (cc)	0.06
BED by LDR (Gy)	135.9

D_{90} - minimal dose (Gy) received by 90% of the prostate, BED - biologically effective dose, V_{100} - the percentage of prostate volume receiving 100% of the prescribed minimal peripheral dose, UD_{30} - minimal dose (Gy) received by 30% of the urethra, R_{100} - rectal volume (ml) receiving 100% of the prescribed dose

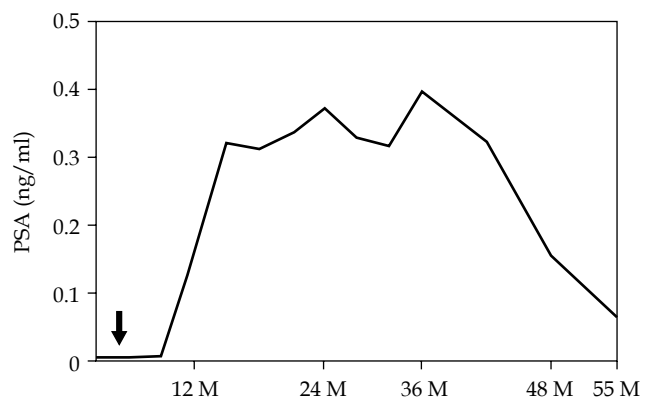


Fig. 4. Prostate specific antigen (PSA) change after the treatment. Y axis shows PSA values. X axis indicates the period (months) after EBRT completion. The black arrow shows cessation of ADT. PSA indicates temporal increase after cessation of ADT, but continuous decrease was observed thereafter. PSA at the latest follow-up (six years after the completion of EBRT) is 0.01 ng/ml: Testosterone level recovered to the normal range value at 9 months after cessation of ADT

(prescription dose). Based on the above-mentioned BED formula, the patient received supplemental EBRT with 45 Gy for whole pelvis (1.8 Gy \times 25 fractions) plus 1.8 Gy \times 1 fraction boost for prostate and seminal vesicle. The purpose of adding one fraction for prostate and seminal vesicle was to achieve a total BED for prostate $\geq 220 \text{ Gy}$.

Therefore, the total BED based on the above-mentioned formula in the present case was 224.8 Gy (135.9 Gy by LDR + 88.9 Gy by supplemental EBRT). Adjuvant ADT was administered for six months after LDR brachytherapy. The total period of ADT was one year. Figure 4 shows a change in PSA value after completion of EBRT. PSA demonstrated temporal increase after cessation of ADT, but continuous decrease was observed thereafter. PSA at the latest follow-up (six years after completion of EBRT) was 0.01 ng/ml. There was no grade 2 genitourinary (GU) and gastrointestinal (GI) toxicity during follow-up. Moreover, there was no evidence of hematuria, nor rectal bleeding was observed throughout follow-up. The patient stayed healthy without biochemical failure, and

without bowel and urinary difficulties at six years. For individual data usage including images and medical history, the author had obtained a written informed consent from the patient.

Discussion

Prostate cancer with nodular bladder invasion (stage T4 prostate cancer) is an extremely difficult clinical entity to achieve a complete cure. The literature on T4 prostate cancer is very limited. Given the relative rarity of T4 prostate cancer, the level of evidence to guide its management is of low quality [7].

Several statistical data or review papers on clinical T4 prostate cancer consistently reported poor prostate cancer specific survival for this disease category [7,8,9,10]. It was repeatedly stated that although there is some survival benefit using prostatectomy, very high-risk patients would still experience poor outcome despite aggressive therapy [7,8,9,10]. Mano *et al.* concluded that such patients may benefit from a local definitive treatment, offering possible cure in a selected patients [9].

Thus, unfortunately, even in this era, no literature has indicated an optimal treatment for stage T4 prostate cancer.

As far as the author is concerned, there has been no clear report demonstrating a complete cure of prostate cancer with nodular bladder invasion. We have previously shown outstanding clinical outcomes by dose escalation for high-risk and very high-risk prostate cancer, including five pelvic lymph node metastasis cases, where BFFS rate of 95.2% was observed at 5 years, using LDR brachytherapy in combination with EBRT of BED \geq 220 Gy [1]. The present report was the detailed case report of the single T4 case derived from our previous report [1].

Among the author's 1,238 brachytherapy cases, the number of T4 disease was only this single case. According to the author's most recent data on 831 brachytherapy-based radiotherapy cases, with minimum follow-up period of two years, 31 cases showed pre-treatment PSA \geq 40 ng/ml (median, 55 ng/ml; range, 40.1-356 ng/ml). Seven cases presented pre-treatment PSA \geq 100 ng/ml. The median follow-up period of the 31 cases was 42 months (range, 24-96 months). Distribution of clinical stage showed T3a (19 cases), T3b (10 cases), and one case of T4 disease. Among the 31 cases, seven patients presented with N1 disease. All these 31 cases received LDR brachytherapy in combination with EBRT of BED \geq 220 Gy; 23 cases received WP EBRT. These twenty-three WP EBRT cases were treated using the same protocol as the present case, although the number of seminal vesicle seed implantation varied according to the degree of seminal vesicle involvement in each case.

Up till now, no biochemical failure and no prostate cancer death among the 31 patients were observed (pre-treatment PSA \geq 40 ng/ml); however, much longer follow-up is mandatory to draw any conclusion (unpublished data). The present case study, combined with our previous report [1], highlights that LDR brachytherapy in combination with WP EBRT of BED \geq 220 Gy is an optimal treatment for prostate cancer with nodular bladder invasion, stage T4 prostate cancer. Moreover, this way of treatment if conducted properly, provides minimum toxicity for the patient.

Conclusions

LDR brachytherapy in combination with WP EBRT of BED \geq 220 Gy is an optimal treatment for prostate cancer with nodular bladder invasion, stage T4 prostate cancer.

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Disclosure

Keisei Okamoto solely designed the treatment plan including the number of seminal vesicle seed implantation and the number of WP EBRT fractions and prostate and seminal vesicle boost EBRT fractions and total BED.

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