Low Dose Rate Brachytherapy for Prostate Cancer

Subjects: Others

Contributor: Manabu Kato , Shinichiro Higashi , Yusuke Sugino , Shinya Kajiwara , Shiori Tanaka , Goshi Kitano , Yasuhumi Yamashita , Yuji Ogura , Hiroyuki Tachibana , Takahiro Kojima , Takahiro Inoue

Low-dose-rate (LDR) brachytherapy was introduced to treat prostate cancer (PCa). Since then, it has been widely applied worldwide, including in East Asia. LDR brachytherapy has been performed in 88 institutes in Japan. Beneficial clinical outcomes of LDR brachytherapy for intermediate-to-high-risk PCa have been demonstrated in large clinical trials.

prostate cancer brachytherapy low-dose-rate brachytherapy

1. Introduction

The prevalence of prostate cancer (PCa) in men is increasing worldwide owing to the aging population and the widespread screening for prostate-specific antigen (PSA); these factors have resulted in PCa having the highest recorded morbidity rate among all male-related malignancies [1]. In 2015, PCa was the leading type of male-related cancer, followed by stomach and lung cancers [2]. This trend has also been observed in Japan.

Surgical intervention, external beam radiotherapy, proton therapy, heavy ion radiotherapy, low-dose-rate (LDR) brachytherapy, high-dose-rate brachytherapy, and active surveillance are generally used to treat localized PCa (https://www.auanet.org/guidelines-and-quality/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022 (accessed on 4 November 2023)) [3]. Among these treatment options, LDR brachytherapy is preferred for patients with PCa who are older or have poor tolerance to treatment. Barringer invented and reported this method for the first time in 1917 (Barringer BS. Radiation for the treatment of bladder and prostate carcinomas JAMA 1917; 68:1227–1230). Since then, the procedure for LDR brachytherapy has been improved, and sophisticated methodologies have been introduced over the years, leading to the procedure being widely used worldwide with good clinical outcomes [4][5]. Barringer predicted that surgery for PCa could become extinct in the future. This claim has not been in the spotlight for many decades; however, with the advent of tri-modality therapy comprising hormone therapy, brachytherapy, and external beam radiotherapy for high-risk PCa and its favorable clinical outcomes, it may be a viable goal.

2. Clinical Outcomes of Localized Low-to-Intermediate PCa Treatment

Brachytherapy is considered an effective treatment option for patients with localized PCa. (https://www.auanet.org/guidelines-and-quality/guidelines/clinically-localized-prostate-cancer-aua/astro-guideline-2022 (accessed on 4 November 2023)) The American Brachytherapy Society has stated that brachytherapy is a convenient, effective, and well-acceptable treatment for localized PCa [6]. However, despite its advantages, brachytherapy cannot be performed in all clinical institutes, leading to the impression of this treatment as a “minor” option. One large review from Japan showed a median follow-up duration of 75 months and 7-year biochemical recurrence-free survival rates of 98%, 93%, and 81% in patients with low-, intermediate-, and high-risk PCa, respectively [5][7]. The indications for combination therapy in the study were as follows: low-, intermediate-, and high-risk PCa should be treated with brachytherapy alone, brachytherapy combined with irradiation therapy, and brachytherapy combined with neoadjuvant androgen deprivation and external radiation therapy, respectively [5][7]. The clinical outcomes of localized low-to-intermediate PCa treatment in the institutes are consistent with the general outcomes of brachytherapy for low-to-intermediate PCa, as reported in these reviews [5][7]. Therefore, the high biochemical recurrence-free survival rate indicates that low-to-intermediate-risk PCa could be controlled using LDR alone or LDR combined with external radiation therapy under appropriate treatment selection. In addition, most Japanese institutes employ radiation oncologists to decide the seed implant position before initiating needle puncture. The seeds are repositioned during the puncture and implantation procedures. This dynamic dose calculation method might produce sufficient dose distribution and good clinical outcomes [8] compared to other procedures in which urologists puncture the prostate before planning seed placement, a process mainly led by radiation oncologists [9]. One randomized study (RTOG0232) for intermediate-risk PCa, particularly in the GS6 and PSA 10–20, and the GS7 and PSA < 10 groups, found no significant difference in biochemical recurrence-free survival (biochemical failure) between brachytherapy combined with external beam radiation therapy and brachytherapy alone (88.0% vs. 85.5% at 5 years). However, there was a significant difference in grade 2 or higher genitourinary (GU) or gastrointestinal (GI) toxicities (42.8% vs. 25.8% in G2, 8.2% vs. 3.8% in G3 at 5 years) [10]. As mentioned above, despite some unpopularity and limited institutional procedures, strong evidence of the unchangeability and stability of brachytherapy for low-to-intermediate-risk PCa has been demonstrated.

3. Clinical Trial of Multi-Modality Brachytherapy for Localized Intermediate-to-High-Risk PCa in Japan

Researchers introduce two clinical trials conducted in Japan to evaluate the efficacy of brachytherapy in patients with intermediate- or high-risk PCa, with and without prolonged hormonal therapy. The high-risk group was supplemented with external beam irradiation as part of the tri-modality therapy. The studies also assessed how a combination of these therapies should be implemented for each risk group, a topic that remains unclear. D’Amico et al. reported the clinical benefits of external beam radiation therapy combined with six months of hormone therapy for localized intermediate- and high-risk PCa [11]. However, no studies have examined the effectiveness of long-term hormone therapy combined with brachytherapy to determine the appropriate use of hormone therapy. Regarding hormone therapy, the PROST-QA study assessed the effect of adjuvant hormone therapy on the QOL parameters for patients with PCa [12]. It was shown that significantly worse sexual function, vitality, fatigue, weight gain, gynecomastia, depression, and hot flashes occurred after two years of hormone therapy, whereas less than

one year of hormone therapy demonstrated a significant decrease in these symptoms [12]. Based on these findings, a clinical trial was planned in Japan to find the answer to the clinical question of whether or not combination therapy with nine-month hormone therapy is effective. One study, “Seed and hormone for intermediate-risk prostate cancer (SHIP) 0804”, was designed to examine this issue. SHIP 0804 is a phase III, multicenter, randomized controlled study conducted in Japan that compared brachytherapy with short- and long-term hormonal treatment in patients with intermediate-risk PCa. Both groups received neoadjuvant hormonal therapy for three months. The patients in one group received no further therapy, whereas their counterparts underwent a nine-month adjuvant hormonal therapy. The results of the SHIP 0804 trial could identify the rationale for hormonal therapy in patients with intermediate-risk PCa undergoing brachytherapy [13]. The planned 10-year follow-up in SHIP0804 after brachytherapy has just been completed, and the data are being analyzed accordingly. Furthermore, in the treatment of high-risk PCa, single treatment options such as radical prostatectomy, external beam radiation therapy, and brachytherapy as the initial treatment could lead to treatment failure, including local and biochemical recurrence [14][15]. There is a need for more effective combined treatments with fewer side effects. Since 2010, tri-modality treatment methods such as brachytherapy, external beam radiation therapy, and hormonal therapy have been reported [16][17][18]. The effectiveness of external radiation therapy combined with hormone therapy for high-risk PCa has also been previously reported [19][20]. Nevertheless, the optimal hormone therapy for tri-modality therapy has not been verified. Another trial titled “Tri-Modality therapy with I-125 brachytherapy, external beam radiation therapy, and short-or long-term hormone therapy for high-risk localized prostate cancer (TRIP)” has also matured. This phase III, multicenter, randomized controlled trial also evaluated the efficacy of brachytherapy combined with external beam irradiation with shorter- versus long-term hormonal therapy in patients with high-risk PCa.

4. Salvage Brachytherapy for PCa

Another useful strategy of LDR brachytherapy for PCa is salvage LDR brachytherapy after external beam radiation. Juanita et al. reported the efficacy of salvage LDR brachytherapy in a phase II clinical trial [21]. In the study, patients received external beam radiation therapy with 74 Gy for 30 months before registration. Patients with favorable- or intermediate-risk PCa with PSA < 20 ng/mL, Gleason score < 7, and clinical T stage T2c or lower were included. The last follow-up duration was 5 years, and the disease-free, biochemical recurrence-free, and overall survival rates were 19%, 46%, and 70%, respectively. Yamada et al. reported the efficacy of salvage brachytherapy [22]. In their study, target lesions were detected using 3 Tesla magnetic resonance imaging (MRI) and prostate biopsy with template methods fused to MRI images. Ultrafocal, hemi-salvage, or whole-salvage brachytherapy was performed according to suspected positive PCa lesions. Biochemical PSA failure was observed in 0/3, 1/5, and 3/5 cases at 48 months of follow-up. The biochemical progression-free survival rate was 75% over 4 years. Therefore, salvage focal brachytherapy may be less invasive for small focal procedures.

5. Focal Brachytherapy for PCa

Recently, focal low dose rate (LDR) brachytherapy has been reported for localized PCa [23][24]. Minh-Hanh et al. demonstrated satisfactory five-year biochemical relapse-free, disease-free, and overall survival rates of 96.8%, 79.5%, and 100%, respectively. However, one limitation of that study is that only patients with low-to intermediate-risk PCa were included [23]. Langrey et al. and Laing et al. reported that hemi-prostate gland brachytherapy showed good clinical outcomes, similar to those of whole-gland prostate brachytherapy, in terms of PSA control and overall survival [25][26]. Elliot et al. demonstrated the efficacy of focal LDR brachytherapy. In their study, 26 patients with low-to intermediate-risk PCa were treated with focal brachytherapy, and the data on adverse events and oncological outcomes were retrospectively analyzed. One case of urinary retention and infection was observed in all cases. Nine (37.5%) grade 1 and seven (29.2%) grade 2 urinary dysfunction cases were observed. Eight patients with ED of grade 2 or lower were also observed. A total of 21 patients were evaluated for PCa recurrence using rebiopsy and MRI; none of the patients had PCa relapse. Only one patient showed PSA recurrence, for which radical prostatectomy was performed [27]. The other report showed less genitourinary toxicity in the focal brachytherapy group than in the whole prostate LDR brachytherapy group [24]. Considering these observations, focal brachytherapy is feasible, with good clinical outcomes and low toxicity. Moreover, randomized studies that compare focal therapy of LDR, focal high-dose-rate brachytherapy, and active surveillance for low-to favorable intermediate-risk PCa are currently ongoing, and their protocols have been published [28]. In that study, 150 patients were randomly enrolled and divided according to treatment options. The primary outcomes were the quality of life after treatment and biochemical recurrence-free survival. Based on the results of that clinical trial, evidence for focal LDR brachytherapy alone for low- to intermediate-risk PCa could be established. It is beneficial for urologists to treat patients with PCa using less invasive procedures.

With regard to new-generation PCa imaging methods, prostate-specific membrane antigen (PSMA) scans using positron emitters such as gallium-68 (Ga), copper-64 (Cu), and fluorine-18 (F), measured with positron emission tomography (PET), could detect PCa lesions more precisely [29]. It may be possible to obtain more accurate images of primary PCa lesions by using a combination of MRI and PSMA-PET, which can help urologists to select treatment options more effectively [30][31]. PSMA-PET shows a small mass of PCa cells in the bone and soft tissue [32]. Body-ablative radiation therapy for oligometastatic lesions can suppress advanced PCa in some patients [32]. These new imaging techniques may make it possible to perform focal therapy, as described. These two methods can be combined to improve the current focal therapy procedures for PCa [33][34]. The utility of deformable registrations of PET/computed tomography (CT) and ultrasound to target PCa was demonstrated in this report. This methodology enables physicians to implant seeds more accurately and to recognize diseased lesions, prostate boundaries, and internal gland shapes, which are sometimes difficult to observe. In the future, a new imaging method comprising PSMA-PET, MRI, and more precise ultrasonography could be applied for focal LDR therapy.

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