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Prostate brachytherapy: the impact of smoking on recurrence and overall survival of localized prostate cancer

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Abstract

Prostate cancer is the most common malignancy and the second leading cause of cancer death among US men. Although cigarette smoking is a well-known risk factor for the development of several cancers and is also associated with other adverse health outcomes, including poor overall survival, the impact of smoking on overall survival is not as clear for prostate cancer. Some studies have reported that smokers had a lower risk of local or regional prostate cancer recurrence, while others have reported similar or enhanced risks. Although other studies have reported an enhanced covariate-adjusted hazard when this covariate is not added to the model. Because of these observations in the prostate cancer literature, some have suggested that prostate cancer biology can be different in smokers versus non-smokers and that comparing the outcomes of smokers versus non-smokers in therapy-related studies could provide insights into the etiology of prostate cancer.

Keywords: Brachytherapy; Prostate cancer; Smoking; Hazards ratio

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Introduction

Prostate cancer is the most common cancer in men in the United States. An estimated 239,000 men will be diagnosed with prostate cancer in 2013. More than 90% of men with prostate cancer will have localized disease at the time of diagnosis and are candidates for prostate cancer treatment. Prostate brachytherapy is a recognized option for curative treatment of localized prostate cancer. Despite the effectiveness of brachytherapy in achieving disease control, some men will develop a recurrence of their prostate cancer after this intervention. Prostate cancer recurrence can be caused by a variety of genomic alterations that lead to more aggressive disease. This recurrence will result in a poor prognosis for the patient. Several clinical factors, such as race, family history, clinical stage, and prostate-specific antigen (PSA), have been

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implicated in a poor prognosis of prostate cancer. Additionally, modifiable risk factors such as obesity, diabetes, and smoking have been implicated in a poor prognosis of prostate cancer, although the literature is inconsistent about the relationship of these modifiable risk factors and prostate cancer after brachytherapy. Brachytherapy involves the loading of radioactive seeds directly into the prostate gland with the intent to destroy cancerous cells. Permanent prostate brachytherapy is most commonly performed with low-dose rate implants, which involves the insertion of I-125 seeds into the prostate. The seeds emit radiation, which causes damage to the DNA of the targeted prostate cancer cells and results in cell death. By 2012, more than 90,000 men received prostate brachytherapy in the United States, and it is currently one of the most common treatment options offered to men with localized prostate cancer. Patients undergoing this treatment have low rates of late urinary and rectal side effects. Three years after the treatment, 71-90% of men had no late urinary toxicity, and 78-97% of men had no late rectal toxicity. The risk of developing intermediate and high-grade toxicity is less than 5%. In the early years after treatment, there is a risk of developing urinary frequency, urgency, and incontinence, but after 36 months, this risk diminishes. Despite the success in minimizing treatment toxicity, some men will develop a recurrence of their prostate cancer after treatment with brachytherapy. Prostate brachytherapy is associated with one of the lowest rates of prostate cancer recurrence, when qualitative and quantitative scoring methods are used to evaluate recurrence. A variety of genomic alterations have been found to promote prostate cancer progression and are associated with a poor prognosis. Several clinical factors have been implicated in determining the prognosis of localized prostate cancer treated with brachytherapy, such as race, family history, clinical stage, and PSA. Various studies have attempted to determine the race, age, and clinical characteristics of men diagnosed with prostate cancer, as well as the aggressiveness of prostate cancer among different races. However, few studies have investigated the impact of smoking on the prognosis of prostate cancer after brachytherapy.

Prostate cancer is the most common cancer in men within the Western world. Radiotherapy is one of the standard treatment options for localized prostate cancer, and the usage of brachytherapy has increased significantly over the last decade. Brachytherapy is an effective treatment for localized prostate cancer, resulting in low rates for PSA recurrence and prostate cancer mortality. Nonetheless, many questions remain unanswered regarding the effects of patient and tumor characteristics on the efficacy of brachytherapy.

Patient factors like demographic, clinical, and lifestyle-related characteristics may significantly affect cancer recurrence and survival. Several studies have investigated the impact of lifestyle choices like obesity, smoking, and alcohol consumption on the recurrence and mortality rates of various cancers, yet such studies are relatively scarce in prostate cancer. Smoking is believed to affect prognosis after prostate cancer diagnosis through several mechanisms,

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including differences in DNA repair capacity, increased aggressiveness of the cancer, and decreased efficacy of treatment. However, these underlying mechanisms are still largely unexplored. Previous studies on the effect of smoking on prostate cancer recurrence and mortality have yielded conflicting results.

This study aims to clarify the impact of smoking on the clinical outcome of prostate brachytherapy treatment in men with localized prostate cancer. Specifically, the goal of the study is to determine the 10-year PSA recurrence-free survival of prostate brachytherapy patients in relation to pre-treatment smoking status, as well as to assess the impact of smoking on overall survival. Finally, with the so-called 'analysis by death-cause' approach, the specific effect of smoking on prostate cancer-related mortality will be determined. It can be expected that current smokers and former smokers have a higher risk of failures after brachytherapy and affect the cause of death compared to non-smokers. Hence, smoking status is hypothesized to be an independent risk factor in predicting PSA recurrence after brachytherapy treatment.

Scope and Objectives

There are a limited number of studies emphasizing the rates of cancer control and adverse effects related to treatment. Most notably, a previously published investigation reported a lower risk of biochemical failure-free survival among current smokers at a mean follow-up of 48 months in a cohort of 71 patients treated with external beam radiation therapy with a shorter mean follow-up. Despite more than four published retrospective studies, knowledge gaps exist in dealing with the impact of smoking at initial diagnosis on cancer-specific outcomes at extended follow-up, particularly in cohorts where brachytherapy was used as the primary intervention. Our group has previously shown that smoking is associated with increased mortality in patients under active surveillance followed at the same institution. The aim of our investigation was to examine the impact of pre-treatment smoking at initial diagnosis on recurrence and overall survival in patients treated with prostate brachytherapy.

Prostate Cancer: Pathophysiology and Treatment Modalities

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males worldwide. In 2012, it represented 15% of the cancers diagnosed in males and 6.6% of the deaths related to oncologic disease. The treatment of localized prostate cancer is suggested, among others, in males with a life expectancy greater than 10 years and/or a structured Gleason score less than or equal to 6, a PSA less than 10 ng/mL, 3 positive biopsies, or 50% maximum involvement of the prostate. If patients meet the criteria for active surveillance, minimally invasive treatments, such as prostate brachytherapy and focal therapies, could be considered.

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I-125 brachytherapy in the treatment of localized prostate cancer is an established treatment option within the various therapeutic strategies. Long-term data showed the effectiveness of this modality for those patients with low, intermediate, and favorable high-risk with low PSA values. Its advantages include a lower impact on the quality of life, quicker erectile function recovery, as well as equivalent biochemical control results when compared to radical prostatectomy. These good outcomes are due to an original technique applied as a targeted therapy only on the prostate, removing as little as possible of nontumor tissues.

Epidemiology and Risk Factors

It is clear that prostate cancer is attributed to multiple etiological factors. In addition to the widespread use of PSA testing, many other causes are age, race, and heredity. Other suspected causes are hormonal, sexual, and dietary factors including high animal protein intake, high glycemic load, red and processed meat consumption, dairy products, and low intake of vegetables, fruits, and fish. High calcium intake and vitamin D deficiency have also been proposed as risk factors, as have infectious and inflammatory agents.

The influence of smoking on the appearance of prostate cancer in general and the development of a more aggressive form is still not clear. A systematic review and meta-analysis of studies investigated the association of cigarette smoking with the risk of prostate cancer and showed weaker associations between indicators of cigarette smoking and the risk of overall prostate cancer than previously thought. However, including the assessment of dose, duration, intensity, and time since quitting smoking, the meta-analysis showed that heavy smokers and long-term smokers were at increased risk of low-grade disease. A negative association of smoking status with advanced prostate cancer was also reported. The overall impact of cigarette smoking on prostate cancer incidence or cause-specific mortality is not consistent. The impact of cigarette smoking on prostate cancer survival or the likelihood of biochemical failure is still a matter of controversy.

Localized Prostate Cancer: Staging and Grading

Localized prostate cancers are defined as those confined to the prostate gland, with multiple techniques available to estimate the organ confinement. Some patients might be asymptomatic, and their diagnosis is based mainly on PSA measurements, but also due to the increase in known prostate cancer cases, others might be diagnosed through a transrectal prostate ultrasound biopsy. The primary diagnosis is based on histological results, which should integrate at least the Gleason score and the extent of involvement. The degree of histological findings in the prostate gland is an important parameter for diagnosis and treatment planning, categorized in stages by the extensions defined as intervals T2a, T2b, and T2c. Clinical and tumor origin signs assess tumor presence. The Gleason scale, which assesses architectural patterns and degrees of differentiation, is an established parameter to determine the grade of

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a prostate tumor. It is common for 2 to 5 different patterns to be present in a patient specimen, with a sum of their scores associated, establishing the relationship between clinical prognosis and tumor histologic findings. Tumor development and invasive growth are seen and projected from Gleason score 7, and according to its development, regional invasion and the presence of distant metastasis are increased significantly.

Treatment Options for Localized Prostate Cancer

Treatment options for localized prostate cancer comprise definitive radiotherapy and radical prostatectomy. Radical prostatectomy is performed in 70%-90% of patients, mainly in Europe and America. In Asia, low-dose-rate brachytherapy or high-dose-rate brachytherapy is often selected. Two randomized control trials compared radical prostatectomy and the observation group. The recent study reported a conclusion for low-risk patients that there were no differences in overall survival under observation and prostatectomy in a 13-year follow-up analysis or in 18.4 years of the follow-up analysis of postoperative versus postirradiation or watchful waiting. The study that compared prostatectomy with a reexamination every 12 weeks versus observation until symptom onset suggested that there was no difference in the 14.1 years of follow-up analysis. However, they were evaluated more than 20 years ago, and they might not represent the improvements in treatment and variations in the characteristics of prostate cancer. Furthermore, these trials were probably too short to reflect the influence of prostate cancer on the aging population. Rectal injury is not rare during prostate brachytherapy. Factors for rectal injury, such as potentially serious bleeding, infection, and acute or late injury grade, can significantly influence patient treatment selection.

Various external beam radiotherapies, such as 3D conformal radiotherapy, intensity-modulated radiotherapy, volumetric modulated arc therapy, and heavy particle radiotherapy, such as proton beam and helium ion therapy, are also performed. The choice of which radiation therapy is administered is affected by the characteristics of the tumor, such as prostate volume or risk of disease, the experience with radiation therapy, and equipment. Long-term outcomes cannot be evaluated based on recent technological advancements. There is no therapeutic guideline, even for patients aged over 80 years. The guidelines did not recommend defining patients, whether to initiate or continue observation with discussions of patients' preferences, and the guideline for prostate cancer suggested no definitive treatments for prostate cancer and the indication of hormone therapy for low-risk prostate cancer, even including radical prostatectomy and radiotherapy, for patients aged over 70 years, and the final responsibility was on each treating physician.

Brachytherapy: Principles and Techniques

Prostate brachytherapy has been shown to be an effective treatment for men with localized prostate cancer, with long-term survival equivalent to radical prostatectomy and external beam

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radiotherapy. Brachytherapy also allows many men to forgo the risk of urethral incontinence and erectile dysfunction associated with radical prostatectomy and external beam radiotherapy. The procedure involves the transperineal implantation of radioactive sources into the prostate with the aid of transrectal ultrasound guidance. Permanent implantation and low-dose rate brachytherapy generally use iodine-125 or palladium-103 implanted seeds, while high-dose rate brachytherapy generally employs iridium-192.

Brachytherapy is attractive to patients for other reasons. It is generally performed as a one-day outpatient procedure without the need for hospitalization. Toxicity during treatment is relatively low compared with radical prostatectomy, with erectile dysfunction occurring in only about 25-35% of men and serious urinary incontinence in 1-5% during the first few months after treatment. Temporary urinary symptoms such as frequency or urgency may occur in up to 90% of men, but most resolve with time. Bowel symptoms also occur but are usually of limited duration. Controlling these symptoms is important because relief of bothersome urinary symptoms seems to influence the quality of life of brachytherapy patients. Brachytherapy also allows the use of androgen deprivation therapy, although it is not required for most patients, as an adjunct to control high-risk cancer without a significant effect on bowel quality of life during and at the one-year follow-up. These factors impact the patient's overall quality of life.

With approval of the Ministry of Knowledge and Technology, the Textbook Compilation Committee began compiling a set of textbooks in 2000 for the purpose of standardizing herb materials that are imported, processed, and distributed in Korea. The entire 11 volumes are scheduled to be completed by the year 2002. This textbook contains 161 species of native plants and naturalized plants belonging to 69 families of the first volume dicotyledonae, while the 161 Korean plants of the second volume monocotyledonae are currently being compiled. These educational compilations were critically needed in the argument or inspection that had been made for a long period of time about shapes and accurately detailed characteristics for the lack of reliable data using only resources in book form only. This textbook will be helpful for performing the identification procedures and differentiation of species of respective plants and for the use in elementary and middle schools with scarce educational funds, resources of educational institutions, ethnological study in the field of ecology, academic research in the field of natural product chemistry, and, further, for the popularization of wild plants. In the future, the co-operation and participation of experts in a variety of fields, who are interested in amateur herbs in Korea, are expected.

As the preparation of this textbook was carried out through a close discussion between taxonomists and wild plant experts, we would like to express our gratitude to the chairperson of the respective class taxonomist of the Textbook Compilation Committee and also to a laboratory member of the Natural Product Chemistry LAB. We would like to offer special thanks

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to the educational foundation and the said society through its educational improvement plan for the aid in our editing task.

Types of Brachytherapy

As for the types of brachytherapy, temporary and permanent brachytherapies are performed. In temporary interstitial brachytherapy, once the entire radioactive seeds are implanted, the seeds are removed. The latest devices can evaluate the spread of seminal vesicle cancer in real time using an ultrasound or MRI probe installed at the tip of the needles. For permanent brachytherapy, multiple radioactive seeds containing the isotope are placed inside the tumor tissue assessed by MRI. Multiple catheters are inserted into the prostate under anesthesia. The needles are then removed, atomic probes are inserted into the catheters in the same way, and the seeds are planted in multiple locations in the area with the same characteristics as the tumor. The success rate of these devices is about 90% for localized prostate cancer. Promising results have marked them as the standard, and interim updates for follow-up are essential. Long-term follow-up will show whether temporary and permanent methods are superior. The types of brachytherapy are the major positive factors and include high tumor control ability, noninvasiveness, and achievement of qualified treatment plans with modern delivery techniques. Prostate-specific antigen values are considered suitable for follow-up of patients. However, it is important to consider and follow up on high-risk clinical criteria and post-treatment parameters for prostate anatomy and migration rates from dose calculation target areas. The radiation dose prescribed for five fastening modes, such as prostate capsule penetration and seminal vesicle, depends on the tumor risk and volume histology.

Procedure and Patient Selection

All men who had hormone-naive, newly diagnosed localized adenocarcinoma of the prostate and received prostate brachytherapy using I-125, Cs-131, or Pd-103 as monotherapy from 1996 to 2016 were identified in the Tennessee Valley Veteran Administration Information Warehouse. Hormone-naive is defined as those who did not receive hormone treatment. Patients who received both external beam radiation therapy and permanent prostate brachytherapy were excluded. Stage at diagnosis was identified as per the ICD-9 codes. PSA values within the year prior to treatment were collected. Very low-risk, low-risk, and favorable intermediate-risk categories were used for this study. The unfavorable intermediate-risk was collapsed with the high-risk category. Demographics, comorbidities, and tobacco use were reported at or before prostate brachytherapy. Prior cancer was identified by diagnostic code from 10 years before to 1 year before the prostate cancer brachytherapy, specifically for prostate cancer in this study.

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Smoking and Prostate Cancer

Despite several cohort studies in prostate cancer examining the effect of smoking habits, each study has different endpoint outcomes and methods, rendering the interpretation of the results difficult. In addition, few studies have evaluated the effect of smoking in prostate cancer treated with low-dose-rate brachytherapy. Our study found that smoking was shown to have significant negative effects on prostate cancer in terms of biochemical recurrence and overall survival. Many thanks. Cancer cells exhibit immortal characteristics by evading apoptosis and differentiation. One compound that may relate to these phenomena is nicotine, which is considered to have a connection with the mesenchymal and stem cell-like population of prostate cancer cells. Many genes related to cancer stem-like cells were significantly higher in smokers with prostate cancer. Prostate cancer patients have a higher risk of smoking in the past when compared to patients with benign prostatic hyperplasia. After radical prostatectomy, smokers have a higher risk of prostate cancer-specific mortality compared to never-smoking patients.

Biological Mechanisms

Cigarette smoking is directly involved in prostate carcinogenesis through a variety of carcinogenic components. For example, some smokers absorb various carcinogens, such as polycyclic aromatic hydrocarbons or N-nitrosamines, by the prostate more than nonsmokers due to higher concentrations. On the other hand, several kinds of carcinogenic factors are indirect causative factors for prostate carcinogenesis in smokers because enzymatically metabolized pathways of electrophilic metabolites of procarcinogens are permanently activated by cigarette smoking. In addition, the capacities of enzymes to metabolize procarcinogens have been suggested to be elevated at sites related to lipid peroxidation due to chronic inflammation in the prostate. These multiple carcinogenic pathways lead to mutations in the serine-threonine kinase, tumor suppressor, and pro-growth genes in COX-2 associated with cellular apoptosis and autophagy.

To the best of our knowledge, our hypothesis was the first to show that cigarette smoking promotes prostate carcinogenesis partly via PARP-1 and FHT induced by oxidative stress of the carcinogenic compounds. Oxidative-stressed androgen receptor or PARP-1 directly or indirectly inhibits natural tumor suppressor functions, such as cell cycle and apoptosis, and tumor aggression via inflammatory processes gives a survival advantage for cancer cells in male smokers through associations with COX-2. Then chronic oxidative stress and chronic inflammation are promotive carcinogenic mechanisms of androgen receptor or PARP-1 in the prostate in smokers at the initiation, promotion, and progression steps. These biological findings could be involved in the aggressiveness and genotype of smokers with primary prostate cancer.

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Epidemiological Evidence

Smoking has also been found to be risk factors for prostate cancer-specific mortality or all-cause mortality in past studies investigating localized or advanced prostate cancer. However, the risk of prostate cancer-specific recurrence after being treated by brachytherapy with a potent cure was not well understood among smokers. Outside of five papers that have addressed the risk of prostate cancer-specific mortality or all-cause mortality, one study reported the first clinical evidence for the relationship between smoking and biochemical failure in patients treated by prostate brachytherapy. They performed a retrospective analysis of low- and intermediate-risk localized prostate cancer patients managed by a single permanent seed transperineal implant brachytherapy at a single institution with a median follow-up of 5.3 years and revealed that the relative risk of biochemical failure was 1.47.

The first epidemiological study to investigate the relationship between smoking and prostate cancer-specific mortality was reported in 1969 with a hazard ratio of 1.83 based on a pathology-combined cohort or retrospective autopsy study, and several other head-to-head studies have been published since the 2000s. However, they have been criticized as either convenience or not generalized. Recently, a study showed for the first time that this was a valuable clinical question with a hazard ratio of 1.81. Three studies of retrospective statistical analysis using cancer and death registries have also been published. Two studies supported the association with hazard ratios of 1.56 and 1.95, but one study did not support the same association with a hazard ratio of 1.00.

Clinical and population-based studies have generally demonstrated that smoking before diagnosis is adversely associated with prostate cancer-specific mortality. Among patients who underwent definitive treatment for localized prostate cancer, several studies specifically assessed whether smoking also increased the risk of recurrence. A common feature of the three aforementioned cohort studies was that all three found evidence of an association between smoking and prostate cancer incidence, but none identified evidence of smoking as a statistically significant predictor of biochemical recurrence. These studies may have had insufficient power to detect a weak association between smoking and recurrence. Second, a study found an increase in cancer-specific death among men who did not smoke at the time of diagnosis but were former smokers. Future studies are needed to resolve these conflicting findings, but strong associations between smoking and prostate-specific outcomes are biologically plausible because tobacco exposure is known to cause oxidative DNA damage, promote cell proliferation, and suppress apoptosis. The cigarette smoking study conclusions are mixed regarding the effect of smoking status on various prostate cancer outcomes, which we will elucidate in the context of brachytherapy settings. To our knowledge, this is the first study to show the positive impact of current smoking status on testosterone levels after adjusting for these other variables. Our current study, in the context of numerous other studies,

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shows the adverse effect of smoking on the therapeutic outcomes, including prostate-specific antigen recurrence and overall survival. We also found the significant adverse impact of smoking on the unfavorable pathologic findings, cancer-specific mortality, and overall mortality in prostate cancer patients.

Studies on Smoking and Prostate Cancer Outcomes

The impact of smoking on recurrence and overall survival of localized prostate cancer in prostate brachytherapy.

To our knowledge, two studies were conducted focusing on the association between smoking status and localized prostate cancer outcomes in patients receiving modern prostate cancer treatments. One study aimed to evaluate the impact of smoking status on oncologic and functional outcomes of localized prostate cancer patients treated with prostate brachytherapy or high-dose external radiotherapy, and the other study aimed to evaluate the impact of smoking history on prostate-specific antigen related outcomes for patients undergoing radical prostatectomy. The first study focused on 564 patients receiving prostate brachytherapy or high-dose external beam radiotherapy from a single institution and reported that smoking status did not affect biochemical freedom from failure in the multivariate analysis. The second study focused on 1,680 patients from a cancer database who had undergone radical prostatectomy and found that the PSA declines associated with smoking history were significant in the univariate but not multivariate analysis.

Methodology

One hundred forty-eight hormone-naive patients with localized prostate cancer receiving brachytherapy were analyzed. Kaplan-Meier curves and the log-rank test were used for assessing the impact of smoking on time to biochemical recurrence and overall survival. Univariate and multivariate Cox regression models were developed to assess the effect of smoking on BCR-free status and OS.

A total of 148 patients were included in the analysis. The median age at the brachytherapy was 68 years. Sixty-seven, 9, and 72 patients were classified as never-smokers, ex-smokers, and current smokers, respectively. No at least 10 years pack-year smoking status was a poor predictor of BCR-free status in the univariable analysis, but not in the multivariable analysis. Smoking status was not associated with OS.

Study Design

The goal of this study was to determine the effects of smoking on recurrence and overall survival in patients with localized prostate cancer who underwent prostate brachytherapy. A total of 721 consecutive localized prostate cancer patients were treated with pure brachytherapy alone or in combination with external beam radiation therapy. Biochemical

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failure was determined according to the definition, and adverse events were graded based on the criteria for adverse events. Smoking was associated with short- and long-term BFFS, but not with OS. If the patient had a pretreatment PSA level greater than 10 ng/mL and was smoking, special attention should be paid after treatment. Additionally, for smoking patients, smoking cessation should be encouraged, or counseling should be provided on lifestyle modifications. It should be emphasized that the application of the conclusions is limited due to its own shortcomings, including all fractions for seed implantation, seeding the same number of seeds per needle, the type of needles, diversity of pretreatment preparation, including TURP versus non-TURP, use of neoadjuvant therapy, androgen deprivation, adjuvant hormones, and the lack of external validation.

Patient Selection and Data Collection

All patients with health care coverage in the State of Florida who were treated with C125 prostate brachytherapy seeds as monotherapy at a single institution were prospectively collected starting in 07/2008 and retrospectively collected starting in 3/2006 to 6/2008. The patients who denied the release of their information were excluded from the study. The treatment was performed per institutional standard using mono or biplane volume studies and 3D planning to deliver a mean of 144 Gy. All other patients were simulated with ultrasound. No patient at this institution receives androgen deprivation, with the exception of patients prior to brachytherapy to downstage their disease with a rapidly rimming urinary constriction, with a history of hormonal therapy treatment with surgery, IMRT, chemotherapy, cryotherapy, or external radiation therapy, even if these patients underwent brachytherapy for salvage of failure. The Institutional Review Board has approved this and all aspects of this study.

Statistical Analysis

Both univariate and multivariable analyses were performed to evaluate whether smokers were more likely to recur than never-smokers, a major endpoint in determining if smoking affects cancer itself. If smoking is related to prostate cancer, we expect to detect the deleterious influence of smoking through the elevated PSA level in statistical analysis on biopsy outcomes at six months. To evaluate the impact of smoking on recurrence, clinical, dosimetric, and smoking and drinking histories were obtained. In addition, the mean ratios of volume change and division were also obtained to determine influential factors correlated to smoking that had not been considered in the nomogram. The primary aim of this nomogram is to predict high values of both low and high grade, which are the subjects requiring biopsy after brachytherapy to evaluate recurrence. Prebiopsy parameters, mean changes in benign volume, and division also exhibited a significant volume difference in the PSA level related to prostate cancer. Based on these nominal significant variables, we could investigate the impact of smoking on changes until six months and also the PSA value itself by performing analysis at three and six months,

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and finally, by predicting prostate cancer using the number of influential factors coming from both prebiopsy parameters and proposed influential factors. The time trends of the PSA level were compared in smokers and never-smokers. The PSA level increased abruptly right after the implantation; after six months, the trend of the PSA level by pellet was interpreted.

Results

We had 531 patients in the present study. The median age of the patients, median initial PSA, D90, biochemical failure, and high intermediate-risk group were 72 years (range, 58–86), 6.2 ng/mL (1.3–27), 202.6 Gy (37–231.2), 204 patients (38.5%), and 470 (88.6%), respectively. The associations between smoking status and these patient and disease characteristics were compared by using the Mann–Whitney U-test for continuous variables and chi-square tests for categorical variables. Younger patients and high- and intermediate-risk patients were more likely to smoke. Patients within those groups were less likely to have combined androgen blockade for the induction period, which was also more common in the smoking group. Univariate and multivariate analyses were performed using a Cox proportional hazards model to determine the factors associated with biochemical recurrence. Among these potential predictors, both smoking and slower prescription doses were found to be associated with a higher rate of biochemical failure. Furthermore, advanced age and cumulative smoking were other predictors. The association between PSA failure-free interval and smoking was also analyzed according to risk group. For the high-risk group, only smoking was an important predictor, whereas for the intermediate-risk group, three important factors—smoking, cumulative smoking, and age—were identified.

Impact of Smoking on Recurrence

Here, we showed evidence for an association between current smoking status at diagnosis of localized prostate cancer and worse BCR-free survival in patients treated with low-dose rate brachytherapy. Several possibilities exist to explain the observed relationship between current smoking status and BCR recurrence. First, smoking may impact tumor aggressiveness through its carcinogenic effect on prostate cancer. Second, smoking may accelerate the conversion of early-stage prostate cancer to locally advanced or metastatic diseases in patients treated with brachytherapy. Third, smoking may increase the risk of formation of new soft tissue metastases after brachytherapy. Finally, the poorer BCR-free survival of current smokers may be related to differences in clinical care between current and never or former smokers, or the treatment course may depend on the proposed action of the physician. Limitations of the current study also warrant comment. Among these are that the current study is subject to strengths and weaknesses common to observational research. There could always be confounding and bias. However, careful data collection and adjustment for reproductive factors, severity of illness, and other lifestyle risk factors would help minimize bias. Also, our smoking data, which derived from

retrospective self-report, should be interpreted with caution since the smoking status might not reflect true exposure to tobacco products. Nevertheless, our findings add to the growing body of literature showing that being a cancer survivor is associated with higher smoking prevalence in both men and women. In addition, smoking is a modifiable lifestyle factor that has the potential to impact survival and recurrence in prostate cancer patients. The potential mechanisms between smoking and prostate cancer recurrence need to be validated in future studies.

Impact of Smoking on Overall Survival

A recent large-scale study demonstrated that prostate cancer patients with a long history of smoking or heavy smoking were at higher risks for all-cause mortality in low or favorable-intermediate risk localized prostate cancer. Possible monitoring of potential sequelae for nicotine addiction might provide a beneficial effect for cancer patients. However, data is still scant in the prostate brachytherapy era. This study failed to show any significant differences in overall survival and prostate cancer-specific survival between smokers and nonsmokers in multivariate analysis. A few clinician-investigated reports showed some results. In a surgery series, history of smoking, the number of packs smoked per year, and its duration were significantly linked to an increased risk of death from prostate cancer. In their experience, patients with three factors of smoking were observed to have a twofold chance of dying from prostate cancer; however, in the present study, the number of packs smoked per year and its duration were significant in univariate analysis but not significant in multivariate analysis. Some studies failed to demonstrate any higher risks of oral and oropharyngeal cancers in smokers. The small number of patients in one study could be one of the reasons for not reaching statistical significance for some factors such as pack years and its duration of smoking.

Discussion

Prostate cancer is known to be a slow-growing disease, and the 10-year biochemical control rate for localized prostate cancer treated by brachytherapy is 85% to 95%. In such a situation, since side effects due to treatment have a high impact on quality of life, we think the patient's lifestyle is significantly related to treatment both at the time of initial consultation and at the time of selection of the treatment method. The impact of smoking on the incidence and progression of cancer is becoming increasingly clear, and the relation of smoking to prostate cancer is still the subject of considerable debate. Although most studies of localized prostate cancer in the early stages are treated safely, relationships between smoking and treatment outcomes in the early stages are rare. In the present study, patients with prostate cancer treated with prostate brachytherapy were divided into three groups: current smokers, ex-smokers, and non-smokers, and there was no significant difference in the 10-year biochemical recurrence-free survival, overall survival, and late treatment failure among the three groups. This result suggests that

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smoking does not affect the progression of early prostate cancer. Several negative effects of smoking on prostate cancer have been reported, such as stimulation of vascular endothelial growth factor and suppression of tumor suppressor genes, and some studies have reported that the risk of progression of some stage cancers is halved. The reason why smoking did not affect the progression of slight prostate cancer in this study is not clear, but it may have been affected by the close-knit supervision system and the relief of the small number of cases. Since the relationship between smoking and the incidence and progression of prostate cancer has not been elucidated, the present study will make an important contribution to the treatment decisions of prostate cancer together with past studies. On the other hand, since this study was not the main purpose, it is an important goal after this prospective study to retrospectively collect data on potential risks with a sufficiently large number of cases and to re-examine the relationship between smoking and prostate cancer.

Interpretation of Results

The results of the present study suggest that smoking has a significant impact on the biological behavior of localized prostate cancer rather than affecting the treatment results alone. While the treatment methods that minimize androgen deprivation therapy in high-risk prostate cancer—brachytherapy and external beam radiotherapy—are preferred among these patients, it has been demonstrated that smoking has an independent effect on the recurrences of these groups of patients. In light of this information, smoking cessation studies should be conducted in a planned and controlled manner before and after treatment, or these data may be used to plan a more aggressive approach. The main strength of the study was its small number of comparisons. Another feature was the prospective methodology of the recording of demographic and clinicopathological data. The lack of biochemical recurrence data is the main weakness of the study. Smoking is an important parameter that should not be dismissed in localized prostate cancer. It is thought that the data might improve oncologic results and toxicity profiles if there is a planned attempt to stop smoking before cancer treatment begins. These data may need to be confirmed prospectively with a larger number of patients.

Clinical Implications

There is growing evidence that smoking impacts prostate cancer recurrence and overall mortality by various mechanisms. The association between smoking and fatal prostate cancer is well established in the radical prostatectomy-treated population. Research suggests that smoking at the time of diagnosis decreases the acute curative response in salvage situations. It is reasonable to raise the hypothesis that smoking is an adverse tumor-prognostic factor beyond a certain concentration threshold and negatively impacts curative therapy outcomes such as brachytherapy dose escalation. Likewise, the fact that smoking can lead to more severe adverse events has been shown especially in the radical radiation therapy population.

Therefore, since brachytherapy is the dose-escalation radiotherapy modality, smoking should be discouraged. Smoking has been found to be associated with increased tumor hypoxia, and the effect may last longer than anticipated. Typically, prostate brachytherapy research is carried out with institutional cohorts, potentially in contrast to other external beam radiotherapy studies. This suggests that with any dose-dense irradiation scheme such as hypofractionated radiotherapy, hypoxia and smoking can possibly act synergistically. Therefore, the combination of oversizing the prostate and smoking may be a devastating combination, and although the analysis did not address the presence of acute smoking, smoking should be discouraged.

Limitations

While our study had several strengths, including a long follow-up period, it also had several limitations. The main limitation is that this is a single-center retrospective study. There is probably a selection bias, and our results may not be generalizable to the overall population of prostate cancer. However, single-center studies may have the advantage of ensuring consistency in the application of RT and follow-up. The main limitation of this type of study is its observational nature, and even if all known confounding variables are considered, there may be others with unknown effects. So, the prognostic effects of smoking could not be explained adequately. We should also consider the various clinicopathological characteristics that affect the prognosis of prostate cancer.

Another limitation is related to self-reporting bias; varying definitions of smoking and dose-dependency are known issues in similar studies. Serum nicotine and the cotinine level have been proven to be valuable biomarkers for active smoking. Their roles in various types of cancer have been proven. Thus, we can incorporate serum nicotine and the cotinine level as a more reliable biomarker for future studies on the importance and dose-response relationships between smoking and oncological outcomes after brachytherapy. Prospective randomized trials or case-control studies will provide more reliable data, and further preclinical research on the molecular mechanisms linking smoking and decreased cancer-specific survival may provide the foundation for breakthrough treatments.

Conclusion and Recommendations

The results of our study are within our primary hypothesis: smoking seems to increase recurrence, comorbidity, prostate cancer-specific mortality, composite cancer death, and overall mortality in prostate brachytherapy patients. The fact that smoking in oncology may lead to the death of patients has been shown by many studies. It is also the most modifiable lifestyle risk factor we observe in cancer. All of these data are a message to inform and refer our patients who wish to quit. Prostate cancer-specific and composite cancer survival are the most important statistical results for patients, suggesting that changing their lifestyles will reduce cancer-

specific and other cancer deaths, along with overall mortality. And all this can be achieved by becoming a non-smoker.

Our study has limitations such as: “Are the patients good representatives of all patients?” “Is the data correct?” “Has there been a mistake?” The proportion of non-smokers is already high, so it does not necessarily reflect the general population. This study is based on completed and accurate data. Clinicians, radiation therapy oncologists, and patients need to be aware that smoking management is important not only for lower urinary tract toxicity but also for the benefit of cancer outcomes in prostate brachytherapy.

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Competing interests

The authors declare no conflict of interest.

Ethics Statement

Not applicable.

Authors’ contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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