The oncological impact of neoadjuvant hormonal therapy on permanent ^{125}I-seed brachytherapy in patients with low- and intermediate-risk prostate cancer

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Running Head

Neoadjuvant hormonal therapy on brachytherapy

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Abstract

Objectives: Permanent brachytherapy is one of the standard treatments for a localized prostate cancer. The purpose of this study is to determine whether neoadjuvant hormonal therapy (NHT) improves oncological outcomes of patients with localized prostate cancer treated with permanent brachytherapy.

Methods: Between January 2004 and November 2014, 564 patients underwent transperineal ultrasonography-guided permanent iodine-125 seed brachytherapy. We retrospectively analyzed low- or intermediate-risk prostate cancer based on the NCCN guidelines. The clinical variables were evaluated for influence on biochemical recurrence-free (BRF) survival, progression-free survival (PFS), cancer-specific survival, and overall survival (OS).

Results: A total of 484 patients with low-risk (259 patients) or intermediate-risk disease (225 patients) were evaluated. Of these, 188 received NHT. With a median follow-up of 71 months, the 5-year actuarial BRF survival rates of patients who did and did not receive NHT were 92.9% and 93.6%, respectively (p=0.2843). When patients were stratified by risk group, NHT did not improve BRF survival outcomes in low- (p=0.8949) or intermediate-risk (p=0.1989) patients. The duration or type of hormonal therapy was not significant in

predicting biochemical recurrence. In a multivariate analysis, Gleason score, pretreatment prostate-specific antigen (PSA), clinical T stage, and prostate dosimetry, primary Gleason score and positive core rate were significant predictive factors of BRF survival, while NHT was insignificant. Furthermore, NHT did not significantly influence PFS, CSS, or OS.

Conclusions: In patients with low- or intermediate-risk disease treated with permanent prostate brachytherapy, NHT did not improve oncological outcomes. Its use should be restricted to patients who require prostate volume reduction.

Keywords: brachytherapy, iodine-125, prostate cancer, neoadjuvant hormonal therapy

Introduction

Permanent brachytherapy is a standard treatment for patients with localized prostate cancer.[1] It is indicated for low-risk prostate cancer and in select patients with low-volume, intermediate-risk cancers, and is often used in association with neoadjuvant hormonal therapy (NHT) not only to reduce the volume of the prostate, but also to improve oncological outcome in patients with higher-risk features.[2-4] Several reports have demonstrated that hormonal therapy combined with radiotherapy improves oncological outcomes in patients with "locally advanced" prostate cancer,[5-7] while use of hormonal therapy in patients with localized prostate cancer remains controversial. Furthermore, the oncological efficacy of NHT prior to brachytherapy also remains unclear. Although intermediate-risk cancer may be treated by brachytherapy combined with external-beam radiation and/or hormonal therapy with the aim of improving therapeutic efficacy, the efficacy of NHT has not yet been established for patients with either low- or intermediate-risk disease. In this study, we assessed the oncological outcomes of NHT in patients with low- or intermediate-risk prostate cancer undergoing permanent brachytherapy.

Methods

Between January 2004 and November 2014, 564 patients with localized prostate cancer underwent transperineal ultrasonography-guided permanent iodine-125 (^{125}I)-seed brachytherapy at Okayama University Hospital. Based on NCCN guidelines, we defined the indications for permanent brachytherapy as low-risk disease (prostate-specific antigen [PSA] <10 ng/mL and Gleason score ≤6 and cT ≤T2a), intermediate-risk disease (PSA 10-20 ng/mL or Gleason score 7 or cT T2b-T2c), and high-risk disease (PSA >20 ng/mL or Gleason score >8 or cT ≥T3a). Of the 564 patients, 21 patients with high-risk disease, 53 patients who had not been followed up for >2 years, 4 patients who received adjuvant hormonal therapy, and 2 patients who had incomplete records were excluded from this study. We analyzed 484 patients with a minimum follow-up of 2 years. To determine each patient's disease classification, all pathology slides of biopsy specimens from all patients were thoroughly reviewed by 1 pathologist (HY) with genitourinary expertise at our institute.

In our institute, when the prostate volume was >35 mL or an adequate dose-volume histogram could not be calculated in patients with pubic arch interference, NHT was administered for 3 months as a general rule. If the

prostate was not sufficiently reduced, an additional 3-month course of NHT was administered. NHT was given to 4 patients with intermediate-risk disease in the context of a clinical trial (SHIP0804, NCT00664456) and to 11 patients who needed to wait for several months to undergo brachytherapy at the discretion of their urologist.

The pre-planning outpatient procedure was usually performed 1 month before seed implantation using the Variseed 7.1 system (Varian Medical System, Palo Alto, CA). During pre-planning, transrectal ultrasound, which allows volumetric analysis of the prostate gland, was performed in the dorsal lithotomy position. Seed implantation was performed under spinal anesthesia. Seeds were placed one by one transperitoneally through the needles using a Mick Applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY). A prescribed dose of 144 Gy was planned to cover >95% of the planning target volume (prostate with 0-3–mm margins). Prostate dosimetry was obtained by a radiation oncologist based on Day 30 postimplant computed tomography using Variseed software. The dose irradiating 90% of the prostate volume (prostate D90) was recorded. The treatment procedure has been described previously.[8, 9]

Patients were followed routinely with PSA measurements every 3 months

for 1 year, then every 6 months for an additional 4 years, and annually thereafter. Biochemical recurrence was defined based on the 2006 Radiation Therapy Oncology-American Society for Radiation Oncology (RTOG-ASTRO) Phoenix Consensus definition (nadir PSA + 2 ng/mL).[10] Progression was defined as any recurrence at primary site or any metastasis in imaging studies.

Biochemical recurrence-free (BRF) survival, progression-free survival (PFS), cancer-specific survival [11], and overall survival (OS) were calculated using the Kaplan-Meier method, and the log-rank test was used for univariate analysis to compare BRF survival rates. Cox regression analysis was used for multivariate analysis. Clinical variables evaluated for influence on BRF survival included use of NHT, Gleason score, clinical T stage, NCCN risk group, radiation dose, pretreatment PSA, primary Gleason score and positive core rate. For all tests, a p-value of <0.05 was considered statistically significant. The JMP version 10 statistical package was used for data analysis. This study was approved by the Institutional Review Board of our hospital (IRB#1710-007). Written informed consent was obtained from all patients before the initiation of treatment.

Results

Patient characteristics are shown in Table 1. Of the 484 patients analyzed, 259 presented with low-risk disease and 225 presented with intermediate-risk disease based on the NCCN classification. The median age at seed implantation was 67 years (interquartile rage [IQR], 62-71 years), median PSA value before biopsy was 6.7 ng/mL (IQR, 5.1-9.0 ng/mL), and median duration of follow-up was 71 months (IQR, 48-95 months). NHT was performed in 188 patients, and the median duration of NHT was 3 months (IQR, 3-6 months). Of them, the median of prostate volume before and after hormonal therapy was 36.4 ml and 25.0 ml, respectively (a 33.1% reduction); NHT+ group had significantly higher PSA and larger prostate volume but lower positive core rate. (Table 1) A total of 33 patients received combined androgen blockade, and the other 155 patients received an anti-androgen or luteinizing hormone-releasing hormone (LH-RH) agonist alone. Sixty patients (12.4%) in total and 43 patients (19.1%) in intermediate risk group had experienced biochemical recurrence.

The 5- and 10-year BRF survival rates of patients who did not receive NHT were 92.9% and 72.3%, respectively, and those for patients who received

NHT were 93.7% and 77.0%, respectively. No statistically significant differences in BRF survival rates were observed between groups (p=0.2843), or among patients with low-risk and intermediate-risk disease, respectively. (p=0.8949 and 0.1989, Figure 1). Furthermore, neither duration (≤3 months vs. >3 months, p=0.1961) nor type of hormonal therapy (single LH-RH agonist or anti-androgen vs. CAB, p=0.3708) were significantly associated with biochemical failure. In a multivariate analysis, Gleason score, pretreatment prostate-specific antigen (PSA), clinical T stage, and prostate dosimetry (prostate D90), primary Gleason score and % positive core were significant predictive factors of BRF survival, while NHT was insignificant. (Table 2) When limiting into intermediate risk group, Gleason score, T stage and primary Gleason score were identified as significant factors for predicting biochemical recurrence in multivariate analysis, while NHT was not identified as a predictive factor in either type of analysis (Table 3). For the entire cohort, the 5- and 10-year PFS rates for patients who did not receive NHT were 98.1% and 86.1%, respectively, and those for patients who received NHT were 98.0% and 94.4%, respectively (p=0.1469). The 5- and 10-year OS rates for patients who did not receive NHT were 96.9% and 89.8%, respectively, and those for patients who received NHT were 100% and 91.5%, respectively

(p=0.1872). Three patients died of prostate cancer; 10-year CSS rates were 98.5% and 95.7% in patients who did not and did receive NHT, respectively (p=0.9430).

Discussion

In patients with low- or intermediate-risk disease who received permanent prostate brachytherapy, NHT did not improve biochemical recurrence free survival. Neither the duration (≤3 vs. >3) nor type (single vs. CAB) of NHT was significantly associated with biochemical recurrence. Furthermore, NHT did not improve PFS, CSS, or OS.

Several retrospective studies revealed that use of NHT for 3-6 months was not a significant predictor of the biochemical failure-free rate in patients with low-risk or intermediate-risk prostate cancer.[3, 12-14] Our previous retrospective study with a median follow-up of 36.5 months also demonstrated that NHT for volume reduction was not associated with biochemical recurrence (p=0.6109).[15] Furthermore, Henry et al. showed that intermediate-risk patients who received 3-4 months of NHT had poorer biochemical failure-free rates compared to those who did not receive NHT (10-year rate, 70.0% vs. 79.4%, p=0.04).[16] In their

series, these investigators described the presence of confounding factors associated with higher-risk pathological features, such as Gleason score 4+3 or higher percentages of positive cores. Our previous study suggested that primary Gleason grade 4 was a significant predictor of biochemical failure in patients with intermediate-risk prostate cancer.[15] In this study, NHT+ group had significantly lower positive core rate. (Table 1) While a positive core rate was significantly associated with BCR in univariate analysis, it was not one of predictors for BCR in multivariate analysis. (Table 2,3) In contrast, Lee et al. reported 5-year BRF survival rates in high-risk patients treated without and with hormone therapy of 74% and 46%, respectively ($p<0.001$), and that hormonal therapy was identified as a significant factor for improving biochemical recurrence in multivariate analysis. These results were supported by a study conducted by Merric et al., in which hormonal therapy resulted in clinically superior biochemical outcomes when high-risk patients were stratified only by hormonal therapy status.[17, 18]

To describe oncological outcomes, we should focus on CSS and OS in addition to biochemical recurrence. Beyer et al. compared CSS and OS in patients who underwent brachytherapy with NHT (n=464) versus without NHT (n=1,884).[19] With a median follow-up of 4.1 years, OS of patients who received

NHT was significantly shorter than that of those who did not receive NHT, while CSS did not significantly differ between groups. Furthermore, multivariate analysis demonstrated that use of hormonal therapy was an independent predictor of worse survival. Of note, duration of NHT was 6 months or less in 80% in their cohort. These authors suggested that the leading cause of death was cardiovascular disease in both groups and that systemic effects of NHT might have a detrimental effect on OS. Dosoretz et al. showed that NHT for 3-6 months with the aim of prostate volume reduction prior to brachytherapy increased the risk of all-cause mortality in patients ≥73 years but not in those <73 years.[20] Although the causes of death were not available, the researchers suggested these observations might be related to the adverse effects of hormonal therapy on the cardiovascular system. A large retrospective study including 5,411 men with low-risk prostate cancer and 4,365 men with intermediate-risk prostate cancer demonstrated that NHT use significantly increased the risk of all-cause mortality in patients with low-risk disease but not in those with intermediate-risk disease. Interestingly, this association was not valid in men without any coronary artery disease risk factors, a history of diabetes mellitus, hypercholesterolemia, or hypertension.[21] In the majority of

patients with early prostate cancer, the natural history of the disease suggests a relatively lower risk of dying. For these patients, the risks of hormonal intervention may be greater than the small benefit that may accompany treatment. Therefore, we should keep in mind short term NHT be potential for these adverse effects.

NHT for volume reduction is required more frequently in Japan than in western countries because only 1,300 MBq of ^{125}I may be implanted in any given individual due to unique laws in Japan. NHT has been used to reduce prostate volume in our institution, particularly for patients with unfavorable geometry (pubic arch interference) or with a large prostate volume.[8, 22] Ebara et al. examined the prostate volume reduction rate based on the duration and type of hormonal therapy, and suggested prostate volumes ≤60 mL could be reduced to an appropriate size with 3 months of LH-RH agonist therapy.[8] Although the purpose of NHT prior to brachytherapy is prostate volume reduction, it is also expected to enhance radiation therapy efficacy, especially when combined with EBRT.[17] Stone et al. showed that another advantage of NHT was that it significantly reduced the risk of urinary retention for patients with moderate to severe urinary symptoms prior to brachytherapy.[4] In contrast, NHT has often

made implanting seeds difficult, resulting in worse prostate D90s.[23] Furthermore, even with short-term use, NHT may be associated with an increased risk of diabetes and cardiovascular disease, and may have a significant effect on long-term sexual function. Potters et al. reported that the 5-year potency rate for patients treated with permanent prostate brachytherapy as monotherapy was 76%; those treated with combination NHT and permanent brachytherapy had a 5-year potency rate of 52%. Multivariate analysis revealed that NHT predicted impotence.[24] Although permanent brachytherapy is fundamentally advantageous to preserve sexual function, this effect may be compromised by hormonal therapy.

An ongoing prospective randomized study (SHIP0804), in which patients with untreated intermediate-risk prostate cancer in both arms receive 3 months of NHT to facilitate recruitment and reduce potential bias in patient selection, is evaluating the safety and efficacy of 9 months of adjuvant hormonal therapy compared to no adjuvant hormonal therapy.[25] Another ongoing prospective randomized study (RTOG0815) is comparing the OS for patients with intermediate-risk prostate cancer who do and do not receive short-term (6-month) androgen deprivation therapy consisting of an LH-RH agonist and oral

antiandrogen therapy starting 8 weeks before dose-escalated radiotherapy with/without brachytherapy. However, no prospective randomized controlled trials have documented the efficacy and safety of NHT prior to brachytherapy.

Recently, the indication for robotic-assisted radical prostatectomy for localized prostate cancer has been extended, and active surveillance for low-risk prostate cancer has been accepted worldwide; therefore, utilization of radiation therapy, especially brachytherapy, has declined.[26, 27] However, radiation therapy is still the most frequently utilized treatment modality for patients ≥75 years with intermediate-risk prostate cancer.[27] The present study, which included relatively long-term follow-up, did not find any oncological benefit of NHT prior to brachytherapy, but it should be noted that brachytherapy alone yielded excellent oncological outcomes.

This study had several limitations. First, it was a relatively small and retrospective study. Second, the indication for NHT varied, although most procedures were done with the goal of prostate volume reduction. Third, the duration and type of NHT varied. Fourth, we did not evaluate QOL or cardiovascular events related with NHT in this study.

In this study, no oncological advantage of NHT associated with

permanent brachytherapy was demonstrated in patients with low-risk or intermediate-risk prostate cancer. In addition, neither the duration nor type of hormonal therapy was significantly associated with oncological outcome. Although other effects of NHT were not evaluated, its use should be restricted to patients who require prostate volume reduction.

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Conflict of interest

None declared.

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Figure Legends

Figure 1. Biochemical recurrence （BCR） free survival curves of the entire cohort (A), low-risk (B) and intermediate-risk group (C). Red line; patients who received neoadjuvant hormonal therapy (NHT), blue line; patients who did not receive NHT

Table 1. Comparison of baseline characteristics of 484 patients stratified by risk group

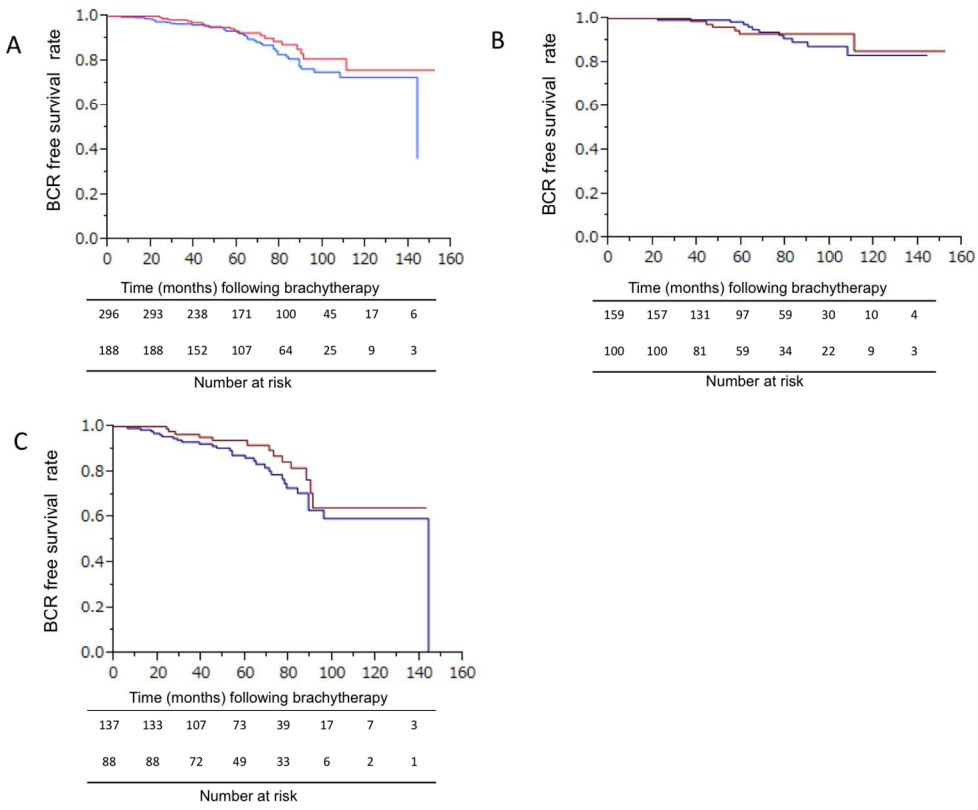
Factor	All patients	NHT(-)	NHT(+)	p
No. of patients	484	296	188	
Median age (IQR)	67 (62-71)	66 (61-71)	67 (63-71)	0.139
Median PSA, ng/mL (IQR)	6.7 (5.1-9.0)	6.7 (5.0-8.3)	7.6 (5.5-10.0)	<0.0001
Median prostate volume pre NHT	29.4(24.1-34.9)	27.2 (22.9 - 30.5)	36.4 (32.1-41.2)	<0.0001
Median prostate volume post NHT	26.3 (21.8-30.4)	-	25.0 (20.0-29.7)	
T stage (%)				0.8097
T1c	306 (63)	184 (62)	122 (65)	
T2a	103 (21)	66 (22)	37 (20)	
T2b	30 (6)	17 (6)	13 (7)	
T2c	45 (9)	29 (10)	16 (8)	
Gleason score (%)				0.1357
6	323 (67)	190 (64)	133 (69)	
7	161 (33)	106 (36)	59 (31)	
Primary Gleason score (%)				0.8886
3	429 (89)	261 (88)	168 (89)	
4	55 (11)	34 (12)	21 (11)	
Median % positive core rate (IQR)		25 (14-38)	20 (13-33)	0.0456
NCCN risk group (%)				0.7240
Low	259 (53)	159 (54)	100 (53)	
Intermediate	225 (47)	137 (46)	88 (47)	
Follow-up, months (IQR)	71 (48-95)	71 (51-96)	71 (47-91)	0.3978

Table 2. Univariate and multivariate analysis for biochemical recurrence free survival of the entire cohort

	Univariate analysis			Multivariate analysis (model 1)			Multivariate analysis (model 2)		
Variables	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Gleason score 7 vs 6	3.360	2.004- 5.710	<0.0001	3.036	1.8001-5.188	<0.001			
T-stage T1 vs T2	2.232	1.339 - 3.720	0.0022	1.77	1.052-2.978	0.0317			
PSA ≧10 vs <10	2.059	1.141 - 3.550	0.0177	1.965	1.067-3.462	0.0309	1.956	1.047 - 3.490	0.0359
NHT (+) vs(-)	0.743	0.423 - 1.263	0.2788	0.619	0.344-1.061	0.086	0.651	0.360 - 1.132	0.1308
Prostate D(90) >140 vs ≦140	0.428	0.254 - 0.7169	0.0013	0.484	0.284-0.814	0.0063	0.487	0.285 - 0.829	0.0081
Primary Gleason score 4 vs 3	3.667	2.056 - 6.281	<0.0001				3.499	1.931 - 6.106	<0.0001
% positive core (unit risk)	5.954	1.708 - 18.24	0.0053				2.797	0.767 - 9.237	0.1158

Table 3. Univariate and multivariate analysis for biochemical recurrence free survival of the patients with intermediate-risk disease

		Univariate analysis			Multivariate analysis (model 1)			Multivariate analysis (model 2)		
Variables		HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Gleason score	7 vs 6	1.824	0.908-4.066	0.0936	2.887	1.303 - 6.947	0.0082			
PSA	≧10 vs <10	1.091	0.573 - 2.013	0.7854	2.032	0.961 - 4.168	0.0631			
T-stage	T1 vs T2	1.916	1.041-3.612	0.0367	2.029	1.089 - 3.871	0.0258	1.429	0.736 - 2.815	0.292
NHT	(+) vs(-)	0.653	0.328 - 1.233	0.1928	0.531	0.257 - 1.040	0.0653	0.655	0.320 - 1.262	0.2116
Prostate D(90)	>140 vs ≦140	0.576	0.310- 1.058	0.0754	0.573	0.305 - 1.064	0.0779			
Primary Gleason score	4 vs 3	2.145	1.138 - 3.947	0.0191				2.079	1.086 - 3.895	0.0277
% positive core (unit risk)		4.414	1.101 - 15.732	0.0367				2.909	0.656 - 11.533	0.1544



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