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The Relationships between Survivals and Early Salvage Androgen Deprivation Therapy for Non-Organ Confined Prostate Cancer after Radical Prostatectomy

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Androgen deprivation therapy (ADT) is one salvage treatment used when prostate-specific antigen (PSA) recurs after radical prostatectomy (RP), especially in high-risk prostate cancer (PC) patients. However, the optimal timing for salvage ADT (SADT) is still unclear. In this study, we analyzed the efficacy of early SADT for non-organ confined PC. We investigated pathologically confirmed, non-organ confined PC patients who received SADT for PSA recurrence after RP. Patients with distant metastasis, those with lymph node involvement confirmed by lymph node dissection, and those who received neo-adjuvant or adjuvant therapy were excluded. Early SADT was defined as ADT initiated before PSA levels reached 0.5 ng/ml from the nadir PSA level after RP. Univariable and multivariable Cox regression analyses were performed for distant metastasis-free, PC-specific, and overall survival. Data from 345 patients were analyzed. The median follow-up duration was 82 months. The median PSA level was 10.9 ng/ml. Patients with T3b or T4 stage cancers represented 24.9% of the cohort; those with a Gleason score ≥9 represented 15.1%. The 10-year distant metastasis-free survival, PC-specific survival and overall survival were 87.1%, 92.0%, 80.9%, respectively. In univariable and multivariable Cox regression analyses, SADT that was initiated when PSA levels were less than 0.5 ng/mL was significantly associated with improved distant metastasis-free survival, PC-specific survival, and overall survival in non-organ confined PC. Early SADT initiated in patients with PSA levels <0.5 ng/mL was associated with increased distant metastasis-free survival, PC-specific survival, and overall survival in non-organ confined PC after RP.

Key Words: *Prostatectomy; Androgen Antagonists; Prostate-Specific Antigen; Salvage Therapy*

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INTRODUCTION

Androgen deprivation therapy (ADT) for prostate cancer (PC) was first introduced decades ago.[1] The efficacy and timing of this therapy for various stages of PC has been investigated by many researchers. In the current National Comprehensive Cancer Network (NCCN) or EAU-ESTRO-SIOG guidelines, ADT is typically reserved for advanced PC.[2,3] Men who received delayed ADT had more symptoms and were more likely to die from PC. However, immediate initiation of ADT improved survival in patients with metastatic PC.[4] Immediate ADT as an adjuvant therapy after radical prostatectomy (RP) for node-positive PC showed improved survival.[5] However, the effect of ADT on node-negative PC is still unclear. In localized PC, men who received primary ADT for PC did not exhibit improved overall survival (OS) over those receiving conservative management.[6] Otherwise, ADT afterlocal curative treatment offers benefits, especially in high-risk PC. In a recent systematic review, early ADT had benefits for PC patients with short PSA doubling times and high Gleason scores.[7] Nevertheless, data regarding optimal timing of ADT as a salvage

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treatment is still limited, despite various suggested regimens. Moreover, although early ADT could delay biochemical and clinical disease progression, the effect of early ADT on survival is still unclear.[8] In this study, we investigated efficacy of early salvage ADT (SADT), or ADT that was initiated before PSA levels reached 0.5 ng/mL, from nadir in non-organ confined PC following RP. We analyzed the impact of SADT on survival outcomes.

MATERIALS AND METHODS

After approval by the Institutional Review Board (No. 4-2017-1206), we retrospectively investigated PC patients who underwent RP within the Yonsei University Health System between 1998 and 2014. We included lymph node-negative, non-organ confined PC patients after RP and who received ADT as a salvage treatment. Non-organ confined PC was classified as T3 or 4 N0 PC after RP. Salvage treatment was defined as ADT or radiotherapy that was provided after PSA elevation from the recorded nadir PSA level after RP. We considered adjuvant therapy to be ADT orradiotherapy provided in the absence of an observed PSA elevation after RP. Patients who received neo-adjuvant or adjuvant therapy were excluded. Patients with metastatic PC at diagnosis and lymph node-positive PC were also excluded. The type and timing of SADT was determined by physician's discretion. Patient's age, body mass index (BMI), prostate volume measured by trans-rectal ultrasonography, PSA level, risk classification, PSA doubling time, and pathological outcomes were assessed as clinical and pathological variables. The D'Amico risk classification[9] was used for risk assessment. PSA doubling time was calculated by comparing PSA level at initiation of SADT and the last PSA level measured before SADT was initiated. Data on mortality and cause of deathwere obtained from Yonsei Cancer Registry Center database at Yonsei University Health System. TNM stage was determined according to the American Joint Committee on Cancer, 8th edition.[10]

We defined early SADT as ADT that was initiated before a change inPSA level reached +0.5 ng/mL over the nadir PSA level recorded after RP. We defined late SADT as ADT provided after PSA level increased more than 0.5 ng/mL over the nadir PSA level. Distant metastasis was defined as metastasis to bone, non-regional lymph nodes, or other sites as reported by radiological evaluation. We defined PC-specific mortality as death caused by PC or PC-related complications.

Cox regression analyses were performed to investigate associations between each clinical parameter and survival. All statistical analyses were performed using SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 345 patients who underwent RP and received SADT contributed to this study. Basic characteristics of this cohort are displayed in Table 1. The median age was 67 years, and the median BMI was 24.2 kg/m^2. Initial median PSA level was 10.9 ng/ml. A PSA level above 20 ng/ml was reported in 62 patients (18.6%). Two-hundred sixteen (216) patients (62.6%) were considered high-risk PC patients as classified using the D'Amico risk classification. After RP, 259 (75.1%) patients had T3a PC, while the remaining 24.9% of patients were T3b or T4 PC. A Gleason score above 9 was observed in 52 patients (15.1%) after RP. A positive surgical margin was recorded for 261 patients (75.7%). Most SADT was performed using a luteinizing hormone-releasing hormone (LHRH) agonist with or without anti-androgen agents. SADT by anti-androgen only was provided in only 45 patients (13.0%).

In the univariable and multivariable Cox regression analyses for distant metastasis-free survival (DMFS), a Gleason score ≥9 was significantly associated with DMFS

TABLE 1. Baseline patient characteristics

n=345	Median IQR	IQR
Age (year)	67	62-71
BMI (kg/m^2)	24.2	22.5-25.8
Prostate volume measure by TRUS (mL)	30	23.0-38.0
PSA (ng/mL)	10.9	7.1-17.2
PSA (categorical) (n/%)		
<20	281	81.4%
≥20	62	18.6%
D'Amico risk classification (n/%)		
Low	28	8.1%
Intermediate	101	29.3%
High	216	62.6%
Pathologic T stage (n/%)		
T3a	259	75.1%
T3b or T4	86	24.9%
Pathologic Gleason score (n/%)		
<9	293	84.9%
≥9	52	15.1%
Positive surgical margin (n/%)	261	75.7%
PSA at salvage ADT (ng/mL)	0.24	0.14-0.96
Type of ADT (n/%)		
LHRH agonist or antagonist with anti-androgens	199	57.7%
LHRH agonist or antagonist only	101	29.3%
Anti-androgens only	45	13.0%
PSA doubling time at ADT (months)	3.4	2.0-6.7
Salvage radiotherapy (n/%)	97	28.1%
BCR after salvage ADT (n/%)	166	48.1%
10 year distant metastasis free survival	87.1%	
10 year prostate cancer specific survival	92.0%	
10 year overall survival	80.9%	

ADT: androgen deprivation therapy, BCR: biochemical recurrence, BMI: body mass index, IQR: interquartile range, LHRH: luteinizing hormone-releasing hormone, PSA: prostate specific antigen, PSM: positive surgical margin, TRUS: transrectal ultrasonography.

(hazard ratio [HR] 4.145, 95% confidence interval [CI] 2.008-8.555), as shown in Table 2. Salvage radiotherapy was also associated with DMFS (HR 0.450, 95% CI 0.220-0.918). Early SADT was significantly associated with improved DMFS (HR 0.108, 95% CI 0.037-0.310). The analysis of PC-specific survival (PCSS) is shown in Table 3. A high Gleason score was associated with PCSS (HR 7.549, 95% CI 2.193-25.983). Early SADT was also associated with improved PCSS (HR 0.098, 95% CI 0.012-0.776). Although salvage radiotherapy was only margin-

TABLE 2. Univariable and multivariable analysis of factors associated with distant metastasis-free survival

Variable	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	0.969 (0.918-1.023)	0.253		
BMI	0.984 (0.842-1.151)	0.843		
Prostate volume measure by TRUS	1.020 (0.997-1.044)	0.090		
PSA		0.110		
<20	1 (ref)			
≥20	0.311 (0.744-1.303)			
Pathologic T stage		0.173		
T3a	1 (ref)			
T3b or T4	1.670 (0.799-3.489)			
Pathologic Gleason score		<0.001		<0.001
<9	1 (ref)		1 (ref)	
≥9	4.915 (2.422-9.977)		4.145 (2.008-8.555)	
Positive surgical margin	0.646 (0.304-1.375)	0.257		
PSA doubling time	0.954 (0.874-1.042)	0.296		
Salvage radiotherapy	0.487 (0.240-0.991)	0.047	0.450 (0.220-0.918)	0.028
Salvage ADT		<0.001		<0.001
Early (PSA at salvage ADT <0.5)	1 (ref)		1 (ref)	
Late (PSA at salvage ADT ≥0.5)	0.090 (0.031-0.257)		0.108 (0.037-0.310)	

ADT: androgen deprivation therapy, BMI: body mass index, PSA: prostate specific antigen, PSM: positive surgical margin, TRUS: transrectal ultrasonography.

TABLE 3. Univariable and multivariable analysis of factors associated with prostate cancer-specific survival

Variable	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.012 (0.919-1.115)	0.804		
BMI	0.861 (0.661-1.121)	0.266		
Prostate volume measure by TRUS	1.021 (0.980-1.064)	0.314		
PSA		0.502		
<20	1(ref)			
≥20	0.494 (0.063-3.863)			
Pathologic T stage		0.037		0.424
T3a	1 (ref)		1 (ref)	
T3b or T4	3.544 (1.078-11.653)		1.671 (0.475-5.878)	
Pathologic Gleason score		<0.001		0.001
<9	1(ref)		1 (ref)	
≥9	9.944 (2.910-33.984)		7.549 (2.193-25.983)	
Positive surgical margin	1.178 (0.312-4.456)	0.809		
PSA doubling time	0.840 (0.677-1.043)	0.114		
Salvage radiotherapy	0.301 (0.087-1.034)	0.056	0.276 (0.080-0.949)	0.041
Salvage ADT		0.013		0.028
Early (PSA at salvage ADT <0.5)	1 (ref)		1 (ref)	
Late (PSA at salvage ADT ≥0.5)	0.074 (0.009-0.580)		0.098 (0.012-0.776)	

ADT: androgen deprivation therapy, BMI: body mass index, PSA: prostate specific antigen, PSM: positive surgical margin, TRUS: transrectal ultrasonography.

TABLE 4. Univariable and multivariable analysis of factors associated with overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.116 (1.050-1.186)	<0.001	1.129 (1.057-1.205)	<0.001
BMI	1.030 (0.885-1.198)	0.705		
Prostate volume measure by TRUS	1.023 (1.000-1.046)	0.049	1.007 (0.983-1.031)	0.595
PSA		0.248		
<20	1 (ref)			
≥20	1.568 (0.731-3.361)			
Pathologic T stage		0.245		
T3a	1 (ref)			
T3b or T4	1.515 (0.752-3.055)			
Pathologic Gleason score		0.002		0.041
<9	1 (ref)		1 (ref)	
≥9	3.054 (1.519-6.141)		2.134 (1.030-4.423)	
Positive surgical margin	0.685 (0.334-1.404)	0.301		
PSA doubling time	1.001 (0.960-1.043)	0.961		
Salvage radiotherapy	1.027 (0.509-2.071)	0.942		
Salvage ADT		0.010		0.006
Early (PSA at salvage ADT <0.5)	1 (ref)		1 (ref)	
Late (PSA at salvage ADT ≥0.5)	0.399 (0.197-0.806)		0.355 (0.169-0.747)	

ADT: androgen deprivation therapy, BMI: body mass index, PSA: prostate specific antigen, PSM: positive surgical margin, TRUS: transrectal ultrasonography.

ally related to PCSS in the univariable analysis (p=0.056, HR 0.301, 95% CI 0.087-1.034), it was associated with improved PCSS in multivariable analysis (HR 0.276, 95% CI 0.080-0.949). In Cox regression analysis for overall survival (OS), OS was associated with older age (HR 1.129, 95% CI 1.057-1.205), higher Gleason score (HR 2.134, 95% CI 1.030-4.423) and early SADT (HR 0.355, 95% CI 0.169-0.747), as shown in Table 4. Collinearity had minimal impact on variables. The variance inflation factor grew from 1.035 to 1.158.

DISCUSSION

This report suggests an impact of early SADT on survival in patients with non-organ confined PC. In this study, early SADT was associated with improved DMFS, PCSS and OS. Current guidelines recommend ADT after RP in node-positive PC.[2] Messing et al.[11] reported that immediate ADT after RP and pelvic lymphadenectomy improved OS and PCSS. Nevertheless, especially in node-negative PC, the effect and timing of ADT after RP has remained controversial. Adjuvant ADT showed improvements in PCSSand systemic progression-free survival after RP in a study reported by Siddiqui et al.[12] However, they reported that the benefits of ADT were lost in the salvage setting. In another study, adjuvant ADT had positive impacts on biochemical progression-free survival and PCSS in T3bN0 PC, but did not show a positive effect on OS.[13]

ADT as a salvage treatment method is still under investigation with regard to its impacts and optimal timing. Moul et al. investigated the effect of early ADT after RP for PSA recurrence. They suggested that early ADT could delay clinical metastasis of PC, but only for advanced PC where the Gleason score was >7 or that PSA doubling time was less than 12 months. They defined "early" ADT as therapy initiated before clinical metastasis was confirmed.[14] The primary end point of that study was clinical metastasis, not OS or PCSS, which might be a limitation. Taguchi et al reported that SADT provided before reaching PSA levels of 0.2 ng/mL could delay biochemical recurrence.[15] However, this study included a relatively small cohort and could not demonstrate a benefit of early SADT for OS or PCSS.

In another study reported in 2016 by Duchesne et al,[16] SADT initiated immediately after a PSA relapse significantly improved OS compared with delayed SADT. They investigated 293 men with PC. Immediate SADT showed better 5-year OS than did delayed SADT (86.4% vs. 91.2%) and did not exhibit differences in treatment-related adverse events. However, this study included patients with PC after variable local therapy, including RP and radiotherapy, and patients without local definite treatments due to patient's age or comorbidity. These inclusions may have affected the study's results.

In previous studies, early SADT in high-risk patients with short PSA doubling time or high Gleason score improved survival.[7] However, its timing remains controversial. In our previous study, we demonstrated the impact of early SADT that was initiated before meeting the clinical definition of biochemical recurrence.[17] We suggested that early SADT had benefits in PCSS in non-organ confined PC. However, we did not investigate OS as an end point in

that study. Moreover, early SADT initiated before biochemical recurrence was not associated with favorable PCSS. This result might be due to the large number of low/intermediate risk groups and patients with Gleason scores <8. These baseline characteristics made is difficult to make an association between PCSS and SADT.

In this study, we tried to suggest an optimal cut-off value for early SADT. We proposed this cut-off value based on our clinical experience. We investigatedvarious levels of PSA, and we found that it was challenging to make significant associations between survival and SADT when PSA levels was lower than 0.5 ng/mL. This finding may be related with the indolent course of localized non-metastatic PC.

The advancement of imaging tools used to detect recurrences and metastases could influence early salvage interventions. Prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET-CT) resulted in a major improvement in patients with biochemical recurrence.[18] This modality can detect recurrence or metastases with more sensitivity, thereby potentially reducing incidence of non-metastatic recurrence. This advancements highlight the potential benefits of early SADT as an intervention for metastatic disease.

This study has a few limitations. First, it is a retrospective study with data collected from a single institution. A prospective, multi-institutional, randomized study is needed to confirm our hypothesis. Second, we assumed cut-off values based on our clinical experience, but a statistically determined PSA cut-off level is necessary for more accurate outcomes. Also, we did not analyze castration-resistant prostate cancer (CRPC) that is one of the important stages in PC. We will try to investigate the association between SADT and the development of CRPC in a future study. Last, we did not investigate any side effects of ADT, like cardiovascular disease or diabetes. Physicians should consider these possible side effects when considering SADT.[19]

Despite these limitations, we have suggested optimal cut-off values for early SADT that were associated with improved survival. This intervention showed favorable relationships for metastasis and OS. Patients may feel anxious when their PSA level rises, so physicians could consider early SADT as a salvage treatment or radiotherapy is PSA level increases are observed.

In conclusion, early SADT was associated with improved DMFS, PCSS, and OS in non-organ confined PC after RP. Thus, physicians may wish to consider early SADT after RP in patients with non-organ confined PC.

Ethics approval and consent to participate

All procedures in our study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. Data were collected after approval from the Institutional Review Board at Yonsei University College of Medicine (No. 4-2017-1206).

CONFLICT OF INTEREST STATEMENT

None declared.

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