Blackwell Publishing

Asian J Androl 2006; 8 (5): 555–561
DOI: 10.1111/j.1745-7262.2006.00175.x

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·Original Article·

Outcomes of locally advanced prostate cancer: a single institution study of 209 patients in Japan

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Abstract

Aim: To investigate the outcomes for Asian populations with locally advanced/clinical stage III prostate cancer (PCa) treated with currently prevailing modalities. **Methods:** We reviewed the record of 209 patients with clinical stage III PCa, who were treated at Niigata Cancer Center Hospital between 1992 and 2003. Treatment options included hormone therapy-combined radical prostatectomy (RP+HT), hormone therapy-combined external beam irradiation (EBRT+HT) and primary hormone therapy (PHT). **Results:** The 5- and 10-year overall survival rates were 80.3% and 46.1% in all cohorts, respectively. The survival rates were 87.3% and 66.5% in the RP+HT group, 94.9% and 70.0% in the EBRT+HT group and 66.1% and 17.2% in the PHT group, respectively. A significant survival advantage was found in the EBRT+HT group compared with that in the PHT group ($P < 0.0001$). Also, the RP+HT group had better survival than the PHT group ($P = 0.0107$). The 5- and 10-year disease-specific survival rates for all cases were 92.5% and 80.0%, respectively. They were 93.8% and 71.4% in the RP+HT group, 96.6% and 93.6% in the EBRT+HT group and 88.6% and 62.3% in the PHT group, respectively. A survival advantage was found in the EBRT+HT group compared with the PHT group ($P = 0.029$). No significant difference was found in disease-specific survival between the EBRT+HT and RP+HT groups or between the RP+HT and PHT groups. **Conclusion:** Although our findings indicate that radiotherapy plus HT has a survival advantage in this stage of PCa, we recommend therapies that take into account the patients' social and medical conditions for Asian men with clinical stage III PCa. *(Asian J Androl 2006 Sep; 8: 555–561)*

Keywords: locally advanced prostate cancer; radical prostatectomy; radiotherapy; hormone therapy

1 Introduction

Until the advent and widespread use of prostate-specific antigen (PSA), prostate cancer (PCa) was essentially an incurable disease for elderly men, and was almost exclusively diagnosed at advanced stages. The PSA test enabled early detection of PCa, and the management of PCa has been considerably improved, especially for early stages, and most PCa cases no longer lead to death [1–5]. Nevertheless, treatment modalities for men with locally advanced/clinical stage III PCa are still a cause for general concern, and consist of the following: radical prostatectomy (RP), radiotherapy and hormone therapy

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Received 2005-11-04 Accepted 2006-02-20

(HT), which are generally used in mono-therapeutic or combined for such stages of PCa. An integrated approach using HT and radiotherapy is becoming the mainstay in North America for clinical stage III PCa, based on a randomized controlled trial that showed a survival advantage of combined adjuvant androgen-deprivation therapy in comparison with radiotherapy alone for men with clinical stage III PCa [1]. However, the study of South West Oncology Group demonstrates better prognostic outcomes using preoperative HT for 4 months followed by RP [2]. Ward *et al.* [3] also showed a favorable result of RP for clinical stage III PCa with a retrospective analysis. In contrast, the Medical Research Council Prostate Cancer Working Party Investigators Group in the UK reported that early primary androgen-deprivation therapy improved survival for men with locally advanced, non-metastatic PCa [4]. Therefore, the optimal therapeutic option for PCa in this stage is a matter of debate.

The nature of PCa is quite different between Asian and the USA or Europe [5–7]. Nevertheless, the treatments for Asian patients with clinical stage III PCa have had to be discussed based on evidence obtained in the USA and Western Europe, because both oncological and andrological outcomes in this stage have scarcely been investigated in Asian countries. In Japan, moreover, the manner of use of HT differs from that in the USA and Western Europe, and it has been widely applied regardless of the extent of disease [5]. In the present study, we first examined the characteristics of patients with locally advanced/clinical stage III PCa in our institution to enhance the understanding of the nature of clinical stage III PCa in Japan and, subsequently, examined the prognostic outcomes and issues which we discussed in terms of currently prevailing treatment modalities.

2 Materials and methods

2.1 Patients and their characteristics

We reviewed the medical record of 221 patients with clinical stage III PCa, who were treated at Niigata Cancer Center Hospital between January 1992 and December 2003. Data of 209 patients were available. Clinical examinations included the PSA test, digital rectal examination, transrectal ultrasound, isotope bone scanning and computed tomography (CT) scan or magnetic resonance imaging (MRI) [8, 9]. Clinical stage was determined according to the TNM classification (UICC1997; primary tumor staging, lymph-node metastasis and distant metastasis).

2.2 Treatment modalities

In the present study, all 209 patients received HT in combination with radical surgery or irradiation, or as a single modality. The patients were sorted into three groups as follows: hormone therapy-combined radical prostatectomy (RP+HT) group, hormone therapy-combined external beam radiation (EBRT+HT) group and primary hormone therapy (PHT) group.

RP was undertaken using a retropubic approach with pelvic nodes dissection by experienced urologists. EBRT was performed using 15-MV photons at an average total dose of 69.1 Gy (range, 60–70 Gy). Patients were scheduled to have a 5-day treatment per week with a daily dose of 2 Gy. The prostatic gland and seminal vesicles were generally included in the initial radiation field with a10-mm margin and up to 50 Gy, and with an additional 20 Gy to the prostate and a 5-mm margin. Some patients received whole pelvis irradiation up to 50 Gy and an additional 20 Gy to the prostate.

PHT involved surgical or medical castration using goserelin or leuprolide, and occasionally combined androgen blockade (CAB) was selected. For CAB, we used the following steroidal anti-androgen, non-steroidal anti-androgen or estrogenic agents: chlormadinone acetate, bicalutamide, flutamide and fosfestrol.

2.3 Statistical analysis

Survival curves were generated using the method of Kaplan and Meier [9]. Univariate and multivariate analyses for survival-associated parameters were conducted using the log-rank test and Cox proportional hazard models. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Primary clinicopathological features

The primary data on the clinical, pathological and treatment-related characteristics of the 209 patients are shown in Table 1. The median follow-up period was 55 months (mean, 56.5 months; range, 2–141 months). Of patients, 30, 78 and 101 underwent RP+HT, EBRT+HT and PHT, respectively. There was a difference in the patients' age between the RP+HT and PHT groups, and 3 patients in the PHT group had a poor performance status score.

3.2 Overall survival rates following each treatment modality

Overall survival rates of these patients are shown in

Table 1. Patients characteristics. RP+HT, hormone therapy-combined radical prostatectomy; EBRT+HT, HT-combined external beam radiation; PHT, primary HT; #, patient number; PS, performance status; Sx, symptoms; grade, biopsy tumor grade; cT, clinical T-stage; pT, pathological T-stage; LND, lymph node dissection; sv, seminal vesicles; NHT, neoadjuvant hormone therapy; AHT, adjuvant hormone therapy, CAB, combined androgen blockade (castration plus antiandrogen). "castration" includes both surgical and medical castration. n.s., not significant. [c]$P < 0.01$, compared with PHT group.

		RP+HT (n = 30)	EBRT+HT (n = 78)	PHT (n = 101)	
Age (years)		64.0 ± 5.1[c]	69.3 ± 5.8	78.1 ± 7.0	$P < 0.01$
PS	0#	29	75	71	
	1#	1	3	27	
	2 or greater#	0	0[c]	3	$P < 0.01$
Sx	Symptomatic#	22	56	81	
	Asymptomatic#	8	22	20	n.s.
PSA (ng/mL)		34.6 ± 28.0	43.8 ± 41.2	53.0 ± 79.9	
	< 10#	6	8	7	
	10–50#	18	49	61	
	> 50#	6	21	33	n.s.
Grade	Well#	8	13	24	
	Moderate#	15	47	58	
	Poor#	7	18	19	n.s.
Gleason score					
	2-6#	8	18	23	
	7#	12	22	31	
	8-10#	5	22	30	
	Unknown#	5	16	17	n.s.
cT	cT3a#	29	73	89	
	cT3b#	1	5	12	n.s.
pT	pT0#	1			
	pT2#	14			
	pT3#	15			
LND	pN0#	24	0		
	pN1#	6	1		
	not done#	0	77		
EBRT					
	Gy 60-64#		3		
	Gy 65-69#		11		
	Gy 70#		64		
EBRT site					
	Prostate and sv#		65		
	Whole pelvis#		13		
NHT PHT duration (months)					
	0 or < 1#	1	9		
	1-3#	6	10	0	
	4-6#	15	19	0	
	7-12#	4	26	0	
	> 12#	4	14	101	
NHT and PHT method					
	CAB#	19	49	51	
	Castration#	8	19	50	
	Antiandrogen#	2	1	0	
AHT duration (months)					
	0 or < 1#	19	7		
	1-6#	0	15		
	7-12#	0	3		
	13-24#	3	7		
	25-36#	0	3		
	> 36#	8	43		
AHT method					
	CAB#	4	14		
	Castration#	7	57		

Figure 1. The 5- and 10-year overall survival rates in all cohorts were 80.3% and 46.1%, respectively. In the RP+HT group, the 5- and 10-year overall survival rates were 87.3% and 66.5%, respectively, and 94.9% and 70.0% in the EBRT+HT group and 66.1% and 17.2% in the PHT group, respectively. A significant survival advantage was found in the EBRT+HT group compared with that in the PHT group ($P < 0.0001$). Also, the RP+HT group had significantly better survival than the PHT group ($P = 0.0107$). There was no significant difference between the EBRT+HT group and the RP+HT group in survival rates. In the PHT group, there was no significant difference between survival rate with CAB and that with castration alone.

3.3 Disease-specific survival rates following each treatment modality

Disease-specific survival rates of these patients are presented in Figure 2. For all participants, the 5- and 10-year disease-specific survival rates were 92.5% and 80.0%, respectively. In the RP+HT group, the 5- and 10-year disease-specific survival rates were 93.8% and 71.4%, 96.6% and 93.6% in the EBRT+HT group and 88.6% and 62.3% in the PHT group, respectively. A significant survival advantage was found in the EBRT+HT group compared with that in the PHT group ($P = 0.029$). There was no significant difference between the EBRT+HT group and the RP+HT group, or between the RP+HT group and the PHT group in survival rates. In the PHT group, there was no significant difference between survival rate with castration and that with CAB.

3.4 Outcomes shown by multivariate analysis

Risk factors for cause-specific mortality shown by multivariate analyses are presented in Table 2. Radiotherapy or RP as well as other clinicopathological factors had little impact on disease-specific survival rates.

3.5 Adverse events

The complications are listed in Table 3. Treatment-related death occurred in one patient in the EBRT+HT group. He died of sepsis resulting from treatment-related rectal bleeding.

4 Discussion

Over the past decade, the PCa treatment strategy has been markedly changed in Japan as well as other countries. HT was previously used for most patients at all stages, but recently, the use of radical treatments such as RP or radiotherapy has rapidly increased [10]. Although several novel radiological local controls assembling technology and methodology have become available [11], the aforementioned options are still therapeutic standards. The life expectancy of patients is an important factor in the decision regarding treatment tools for patients with localized or locally advanced cancer, and the indication for radical or conservative therapy inevitably depends on this unstable factor. Radical treatments have been applied for patients under the age of 70–

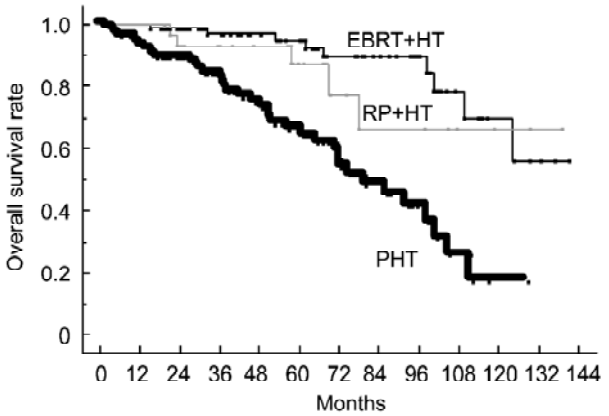

Figure 1. Overall survival curves according to the treatment group. RP+HT, hormone therapy-combined radical prostatectomy; EBRT+HT, HT-combined external beam radiation; PHT, primary HT. $P < 0.0001$ for EBRT+HT *vs.* PHT. $P = 0.0107$ for RP+HT *vs.* PHT.

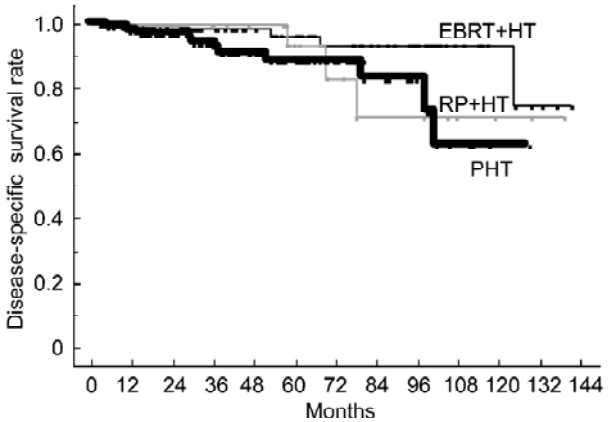

Figure 2. Disease-specific survival curves according to the treatment group. RP+HT, hormone therapy-combined radical prostatectomy; EBRT+HT, HT-combined external beam radiation; PHT, primary HT. $P = 0.029$ for EBRT+HT *vs.* PHT.

Table 2. Multivariate analysis with hazard rates for cause-specific mortality in patients with locally advanced/clinical stage III prostate cancer (PCa). PS, performance status; PSA, prostate-specific antigen; EBRT, external beam radiation; RP, radical prostatectomy. Gleason scores were not available for 38 cases in the earlier period.

Factors	Variables	*P*-value	Risk ratio (95% CI)
Age (years)	≥ 75 / < 75	0.7475	1.386 (0.190–10.118)
PS	1 or greater / 0	0.4697	1.925 (0.326–11.355)
Symptoms	+/–	0.6605	1.617 (0.189–13.815)
PSA (ng/mL)	≥ 50 / < 50	0.4204	1.675 (0.478–5.872)
T-stage	≥ T3b / < T3a	0.3277	3.091 (0.322–29.629)
Gleason score	7 – 10 / 2–6	0.2991	2.394 (0.461–12.435)
Treatment	EBRT –/+	0.3326	0.362 (0.046–2.828)
	RP –/+	0.8943	1.186 (0.096–14.619)

Table 3. Adverse events. #, patient number; RP+HT, radical prostatectomy plus hormone therapy; EBRT+HT, external beam irradiation plus hormone therapy.

	RP+HT	EBRT+HT
Hematuria (grade 3)[#]	0	4
Rectal bleeding (grade 3 or greater)[#]	0	4
Urinary incontinence (pad required)[#]	3	0
Rectal injury (primary closure)[#]	2	0
Urethral stricture (dilation required)[#]	1	1

75 years, whereas conservative treatments, such as HT or even watchful waiting, are preferred as the therapeutic first-line for higher age or complicated cases [10]. Localized PCa is associated with favorable prognosis with either conservative or radical treatments [9–11]. However, the treatment options applied for locally advanced/clinical stage III PCa vary depending on the patient, and even radical surgery or radiotherapy frequently fails to achieve a disease-free status in mono-therapeutic use [12]. Therefore, we have attempted various combined therapies for more than 200 men with this stage of cancer. Although we could only retrospectively assess this trial, the purpose of the present study was to evaluate the PCa treatment in oncological and andrological terms, and we reviewed the details below.

We evaluated the results of prostatectomy, radiotherapy or hormone therapy in patients with clinical stage III PCa. Our outcomes were comparable with those of previous reports [1, 2, 13–15], and the adverse effects were also acceptable. In the present study, radiotherapy combined with HT appeared to be superior to HT alone in terms of overall and disease-specific survival rates. However, this does not directly imply an advantage of the radiotherapy-combined treatment, because the patient characteristics substantially differed in terms of measured prognostic factors and undoubtedly varied in terms of other unmeasured prognostic factors. As presented in Table 1, our hormonal therapy varied with respect to the drug-type and administration period, and our radiotherapy differed with respect to the approach and dose. Also, there were differences in clinical parameters, such as the patient's age and serum PSA level among the compared groups. Therefore, the present comparison does not enable us to draw a definite conclusion, and our results could not show a significant survival advantage when analyzed multivariatively. However, radiotherapy is increasingly applied for localized disease, and novel integrated approaches are being intensively examined [16].

Because of the small number of patients enrolled in the present study, we cannot stress the role of radical prostatectomy for clinical stage III PCa. Although prostatectomy, with its questionable advantage, is not strongly recommended in the guidelines of the USA, a randomized trial conducted in Japan demonstrated rather favorable outcomes for surgery [15]. Accordingly, further studies are required to examine the usefulness of radical surgery in this stage of PCa.

HT alone is a feasible option for complicated or elderly men with clinical stage III PCa [17]. In Japan, primary hormone therapy has been commonly preferred for treating not only metastatic but also non-metastatic disease with relatively encouraging results [5, 18]. The difference in the use of HT between Japan and USA is probably a result of different perceptions of its adverse effects and quality-of-life issues [5]. Some investigators discuss intrinsic oncological differences in PCa treatment outcomes [7, 19]. Prognosis following hormone therapy for Japanese PCa patients is considered to be

better than that for white men in the USA [20]. Therefore, primary hormone therapy for clinical stage III disease might be an applicable option not only for elderly but also younger patients in Asian populations.

Although some previous studies suggest the superiority of radical treatments [21], there has been no prospective study that shows a survival advantage of radiotherapy plus hormone therapy in comparison with hormone therapy alone. A randomized trial currently in progress (CAN-NCIC-PR3), which compares CAB and radiation-combined CAB, might reveal the significance of irradiation in the treatment of clinical stage III PCa [1–3]. Correspondingly, a prospective study concerning the aforementioned issues is warranted for Asian men with clinical stage III PCa. Still, carrying out such a study is expected to be rather difficult, because T3 PCa necessarily involves diagnostic problems when studied multicentrically [1, 3, 8], and retrospective single-institute approaches might be more practical methods.

In conclusion, the present study suggests that HT combined with radiotherapy potentially has a survival advantage compared with primary HT for Japanese men with locally advanced/clinical stage III PCa. However, there is no great difference among currently prevailing treatment modalities, and therapies that take into account the patients' social and medical conditions should, therefore, be selected for Asian men with cancer in this stage. Also, our data does not include information about treatment-related metabolic disorders or sexual dysfunction, but their assessment is of general interest [22]. Therefore, clarifying the roles of surgery, radiotherapy and HT for Asian populations with locally advanced PCa is critical, and well-designed further studies are warranted.

Acknowledgment

The authors thank Drs Yasunosuke Sakata, Manabu Watanabe, Mari Saito, Norio Miyajima, Masaaki Naito, Naoki Arimoto, Toshiyuki Itoi, Kazuhiro Kobayashi, Kazuya Suzuki, Etsuko Tonegawa and Shuichi Komatsu for their enthusiastic contribution to the treatment of patients enrolled in this study.

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Edited by Prof. Shahriar Koochekpour