Postoperative Radiotherapy for Localized Prostate Cancer: Clinical Significance of Nadir Prostate-specific Antigen Value within 12 Months

KAZUHIKO OGAWA[1], KATSUMASA NAKAMURA[2], TOMONARI SASAKI[3], HIROSHI ONISHI[4], MASAHIKO KOIZUMI[5], MASAYUKI ARAYA[4], NOBUTAKA MUKUMOTO[6], MICHIHIDE MITSUMORI[7], TERUKI TESHIMA[6]; and the Japanese Patterns of Care Study Working Subgroup of Prostate Cancer

[1]Department of Radiology, University of the Ryukyus, Okinawa;
[2]Department of Clinical Radiology, Kyushu University at Beppu, Oita;
[3]Department of Radiation Oncology, National Kyushu Center, Fukuoka;
[4]Department of Radiology, Yamanashi University, Yamanashi;
Departments of [5]Radiation Oncology and [6]Medical Physics and Engineering, Osaka University, Osaka;
[7]Department of Radiation Oncology and Image-Applied Therapy, Kyoto University, Kyoto, Japan

Abstract. *Aim: To analyze retrospectively the results of postoperative radiotherapy for localized prostate cancer and to investigate the clinical significance of nadir prostate-specific antigen (PSA) value within 12 months (nPSA12) as an early estimate of clinical outcome after radiotherapy. Patients and Methods: Seventy-six patients with localized prostate cancer treated with postoperative radiotherapy were retrospectively reviewed. Total radiation doses ranged from 50 to 70 Gy (median: 60 Gy), and the median follow-up period for all 76 patients was 47.9 months (range, 12.4-101.3 months). Results: The 5-year actuarial overall survival, progression-free survival, biochemical relapse-free survival (BRFS) and local control rates in all 76 patients after radiotherapy were 86.1%, 77.8%, 80.0% and 92.2%, respectively. Distant metastases and/or regional lymph node metastases developed in 11 patients (14%) after radiotherapy, while local progression was observed in only 5 patients (7%). Of all 76 patients, the median nPSA12 in patients with biochemical failure and that in patients without biochemical failure were 1.16 ng/ml and 0.05 ng/ml, respectively. The 5-year BRFS rates in patients with low nPSA12 (<0.5 ng/ml) and those with high nPSA12 (≥0.5 ng/ml) were 92.7% and 42.2%, respectively (p<0.0001). In univariate analysis, nPSA12, pre-radiotherapy PSA, Karnofsky performance status and the use of chemotherapy had a significant impact on BRFS, and in multivariate analysis, nPSA12 alone was an independent prognostic factor for BRFS. Conclusion: Postoperative radiotherapy results in an excellent local control rate for localized prostate cancer and nPSA12 is predictive of biochemical failure after postoperative radiotherapy.*

Radical prostatectomy has been established as the primary curative procedure for the treatment of localized prostate cancer. However, despite a marked downward stage shift due to widespread serum prostate-specific antigen (PSA) screening and improvement in surgical techniques, approximately one-third of patients who undergo radical prostatectomy for their prostate cancer will experience biochemical recurrence after surgery (1-3). Many reports have indicated that the most significant risk factors for biochemical recurrence after prostatectomy are high Gleason score, extraprostatic extension, seminal vesicle invasion and a positive surgical margin (1, 4-8). Rising PSA levels following radical prostatectomy may be due to a local recurrence in the prostatic bed, occult distant metastases or a combination of both.

Although the optimal postoperative management of patients with localized prostate cancer has not yet been established, postoperative radiotherapy may be considered the treatment of choice to achieve both biochemical and local control (9-13). Recent randomized trials have demonstrated that in men who had undergone radical prostatectomy for pathologically advanced prostate cancer, adjuvant radiotherapy resulted in a significantly reduced risk of biochemical recurrence and disease recurrence compared with observation alone (11, 14).

Correspondence to: Dr. Kazuhiko Ogawa, Department of Radiology, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan. Tel: +81 988953331(ext. 2401), Fax: +81 988951420, e-mail: kogawa@med.u-ryukyu.ac.jp

Key Words: Surgery, prostate cancer, nPSA12, radiotherapy, biochemical failure, prognostic factor.

However, little information regarding clinically useful markers of recurrence risk exists for prostate cancer patients who undergo postoperative radiotherapy.

For patients with untreated prostate cancer, PSA has been utilized as an important marker for treatment response and disease recurrence for prostate cancer (15, 16). The nadir in PSA (nPSA) after radiotherapy has been shown to predict biochemical failure (17, 18), distant metastasis (19, 20), cause-specific mortality (21, 22) and overall mortality (22). However, the nPSA usually takes several years to occur, even as long as 8-10 years in some patients, and as a consequence, nPSA has little practical clinical value. It would be ideal to identify a surrogate nPSA that describes the lowest PSA achieved during a well-defined, relatively short time interval after completion of radiotherapy. Recently, time-limited survey of PSA, such as nPSA value within 12 months (nPSA12), has been reported to be an early predictor of biochemical failure, distant metastasis and mortality that is independent of radiotherapy dose and other determinants of outcome after radiotherapy for previously untreated localized prostate cancer (15, 16).

Because nPSA12 has been shown to be a useful predictor of treatment outcome for untreated localized prostate cancer treated with radical radiotherapy, we hypothesized that nPSA12 may also have potential applications in the monitoring of localized prostate cancer treated with postoperative radiotherapy. In the current study, we first analyzed the treatment results of postoperative radiotherapy for patients with localized prostate cancer. Next, we examined the nPSA12 level in patients with localized prostate cancer treated with postoperative radiotherapy and investigated whether nPSA12 could be a prognostic factor of clinical outcomes for these patients.

Patients and Methods

We used the detailed data from patients with localized prostate cancer who were included in the Japanese Patterns of Care Study (PCS). The PCS, which has been developed in the United States as a quality assurance program, was conducted in Japan in an attempt to obtain data on the national standards of radiotherapy for several diseases including prostate cancer (23). The Japanese PCS Working Subgroup of Prostate Cancer initiated a nationwide process survey for patients who underwent radiotherapy between 1996 and 1998. Subsequently, a second PCS of Japanese patients treated between 1999 and 2001 was conducted. We have previously reported the results of the first and second PCS surveys with respect to postoperative external beam radiotherapy for prostate cancer patients (24).

PCS methodology has been described previously (23, 25, 26). In brief, the PCS surveys were extramural audits that utilized a stratified two-stage cluster sampling design. The PCS surveyors consisted of 20 radiation oncologists from academic institutions, and each radiation oncologist collected data by reviewing patients' charts from their institution. Patients with a diagnosis of adenocarcinoma of the prostate were eligible for inclusion in the present study unless they had one or more of the following conditions: i) evidence of distant metastasis; ii) concurrent or prior diagnosis of any other malignancy; iii) prior radiotherapy. The PCS data used in the current study are from two Japanese national surveys conducted to evaluate prostate cancer patients treated with radiotherapy in the 1996-1998 and 1999-2001 PCS surveys. Of the 839 patients comprising the 1996-1998 and 1999-2001 PCS survey populations, a total of 169 patients who received postoperative radiotherapy after radical prostatectomy were identified. Of these, 93 patients with insufficient nPSA12 data and/or patients who received total doses of less than 50 Gy were excluded, and in total, 76 patients with measurable nPSA12 were subjected to this analysis. The disease characteristics of these 76 patients, such as the tumor stage and pre-treatment PSA levels, were not significantly different compared to those of 93 patients having insufficient data for nPSA12 and/or those who received total doses of less than 50 Gy. All 76 patients received surgical resection initially, followed by postoperative radiotherapy.

Table I shows the patient characteristics of all 76 patients. Postoperative radiotherapy was administered as an adjuvant therapy (undetectable PSA and postoperative radiotherapy in 3-12 months after surgery) to 42 patients and the remaining 34 patients received radiotherapy as salvage therapy (elevated PSA and/or delayed rise in PSA after surgery). PSA was defined as the PSA value before initial treatment and pre-radiotherapy PSA was defined as the PSA value just before radiotherapy.

The method of treatment is shown in Table II. Hormonal therapy was administered either alone or in combination with orchiectomy, estrogen agents, luteinizing hormone-releasing hormone (LH-RH) agonists or antiandrogens after radiotherapy. The median duration of hormonal therapy was 15.4 months (range, 0.1-77.6 months). Regarding chemotherapy, 11 patients (14%) were also treated with chemotherapy, such as estramustine and 5-fluorouracil.

Regarding radiotherapy, the majority of patients were treated with >10 MV linear accelerators and also treated with 4 or more portals. The median radiation dose delivered to the prostate bed was 60 Gy (range, 50-70 Gy), and the median dose per fraction was 2 Gy (range, 2-2.2 Gy). Thirty patients (39%) received treatment to the pelvic nodes in addition to prostate bed, and the remaining 46 patients (61%) received irradiation only to the prostate bed. Regarding lymph node status, 6 out of 7 patients (86%) with pathologically positive lymph nodes received treatment to the pelvic nodes in addition to prostate.

nPSA12 was defined as the lowest PSA level achieved during the first year after completion of radiotherapy. The median number of PSA evaluations within 12 months after radiotherapy was 4 times (range, 1-17) in all 76 patients. The median follow-up of all patients was 47.9 months (range, 12.4-101.3 months), and all patients without biochemical failure had at least 1 year's follow-up. Biochemical failure is defined according to the Phoenix consensus definitions: failure is considered when PSA levels reach 2 ng/ml or more above nadir (27). Concerning clinical failure, patients were categorized as having progression after radiotherapy if they developed local, pelvic nodal, or distant failure. Alone or combination of chest radiography, liver ultrasound, computed tomography scans and magnetic resonance imaging scans were used for confirmation of suspected progression.

Statistical analyses were performed using the Statistical Analysis System at the PCS statistical center (28). Overall survival,

Table I. *Patient characteristics*.

	No. of patients
Age (median: 67.0116 years)	
<70	51
≥70	25
Type of therapy	
Adjuvant	42
Salvage	34
Surgical margin	
–	31
+	15
Unknown	30
Capsular invation	
–	15
+	34
Unknown	27
Seminal vescicle invation	
–	30
+	14
Unknown	32
Pathological T stage	
T0-2	11
T3-4	62
Unknown	3
Pathological N stage	
N0	52
N1	7
Unknown	17
KPS (%)	
≤80	17
>80	58
Unknown	1
Pre-treatment PSA (ng/ml)	
Median (range)	14.7 (0.0-268.2)
<20	40
≥20	29
Unknown	7
Pre-radiotherapy PSA (ng/ml)	
Median (range)	0.6435 (0.01-22.90)
<2	42
≥2	12
Unknown	22
Gleason combined score	
≤6	24
>6	19
Unknown	33
Differentiation	
Well/Moderate	49
Poor	22
Unknown	5

KPS, Karnofsky performance status; PSA, prostate-specific antigen.

Table II. *Treatment characteristics*.

	No. of patients
Radiation field	
Whole pelvis plus boost	30
Prostate only	46
CT-based treatment planning	
Yes	63
No	13
Conformal therapy	
Yes	30
No	40
Unknown	6
Total radiation dose (Gy)	
<60	30
≥60	46
Use of hormonal therapy	
Yes	57
No	18
Unknown	1
Use of chemotherapy	
Yes	11
No	62
Unknown	3

KPS, Karnofsky performance status; PSA, prostate-specific antigen.

progression-free survival (PFS), biochemical relapse-free survival (BRFS) and local control rates were calculated actuarially according to the Kaplan-Meier method (29) and were measured from the start of radiotherapy. Differences between groups were estimated using the chi-square test, Student's *t*-test, Mann-Whitney *U*-test and the log-rank test (30). Multivariate analysis was performed using the Cox regression model (31). A probability level of 0.05 was chosen for statistical significance. The Radiotherapy Oncology Group (RTOG) late toxicity scales were used to assess the late morbidity (32).

Results

Seven out of 76 patients (9%) died during the period of this analysis. Of these patients, 6 patients died of prostate cancer and the remaining 1 patient died without any sign of clinical recurrence (intercurrent diseases). The 5-year actuarial overall survival, PFS, BRFS and local control rates in all 76 patients after radiotherapy were 86.1%, 77.8%, 80.0% and 92.2%, respectively (Figures 1 and 2). With regard to the site of recurrence, 15 patients had clinical failure (local only in 3, local with distant metastases in 2, regional in 1, distant metastasis in 7, regional and distant metastasis in 1 and unknown site in 1 patient). Distant metastases and/or regional lymph node metastases developed in 11 patients (11%) after radiotherapy, while local progression was observed in only 5 patients (7%). Regarding the total radiation dose (Table III), 51 out of 56 patients (91%) treated with less than 66 Gy achieved local control, while 20 out of 20 patients (100%) treated with 66 Gy or more achieved local control (p=0.17). Regarding the radiation field used, 28 out of 30 patients (93%) treated for the whole pelvis with boost and 43 out of 46 patients (93%) treated with a local field achieved local control; this difference was not statistically significant (p=0.98).

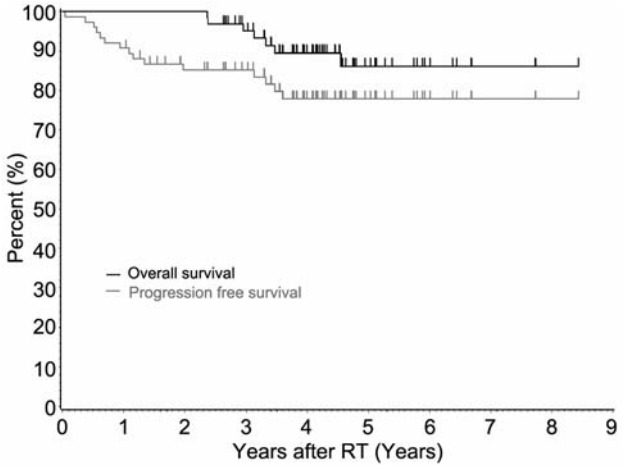

Figure 1. *Actuarial overall and progression-free survival curves for 76 patients with prostate cancer treated with postoperative radiotherapy.*

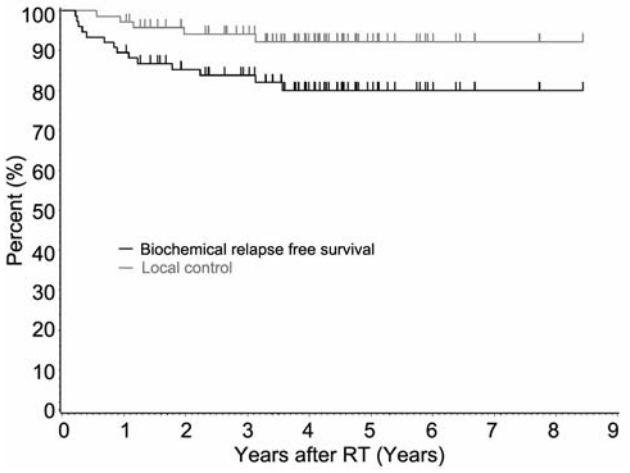

Figure 2. *Actuarial biochemical-free survival and local control curves for 76 patients with prostate cancer treated with radiotherapy.*

Table III. *Local control according to the radiation dose and field.*

Total dose (Gy)	No. of pts	No. of pts with LC	Incidence of LC	
			WP + B	Local
50-59.9	30	28 (93%)	18/19	10/11
60-61.9	23	21 (91%)	9/9	12/14
62-63.9	0	0	0/0	0/0
64-65.9	3	2 (67%)	1/2	1/1
66-67.9				
68-69.9	9	9 (100%)	0/0	9/9
70	11	11 (100%)	0/0	11/11
Total	76	71 (93%)	28/30 (93%)	43/46 (93%)

Pts, Patients; LC, local control; WP, whole pelvis; B, boost.

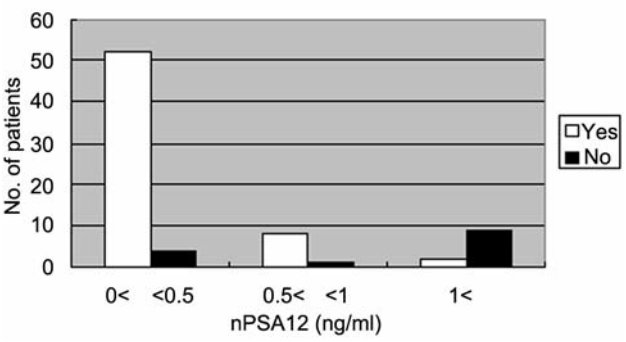

Figure 3. *Distribution of nPSA12 values according to biochemical control (yes: controlled, no: not controlled). Over 80% of patients with biochemical control had a nPSA12 <0.5 ng/ml, while only 29% of patients who experienced biochemical failure had a nPSA12 <0.5 ng/ml.*

Of all 76 patients, the median nPSA12 in patients with biochemical failure and that in patients without biochemical failure were 1.16 ng/ml and 0.05 ng/ml, respectively. Patients treated with adjuvant therapy had significantly lower nPSA12 (median: 0.07 ng/ml) than those treated with salvage therapy (median: 0.23 ng/ml, p=0.018). On the other hand, patients treated with hormonal therapy had almost similar nPSA12 (median: 0.10 ng/ml) compared to those without hormonal therapy (median: 0.09 ng/ml, p=0.45). Figure 3 shows the distribution of nPSA12 according to the achievement of biochemical control. Over 80% of patients with biochemical control (52 out of 62 patients, 84%) had a nPSA12 of <0.5 ng/ml, while only 4 patient out of 14 patients (29%) with biochemical failure had a nPSA of <0.5 ng/ml (p<0.0001). For the 52 patients who achieved a nPSA12 level <0.5 ng/ml and who did not experience biochemical failure, the median time from the completion of radiotherapy to achievement of a nPSA12 level <0.5 ng/ml was 2.0 months (range, 0.2-11.5 months).

When dividing patients into low (<0.5 ng/ml) and high (>0.5 ng/ml) nPSA12 groups, the 5-year BRFS rates in patients with low nPSA12 and those with high nPSA12 were 92.7% and 42.2%, respectively (p<0.0001) (Figure 4). In univariate analysis, nPSA12, pre-radiotherapy PSA, Karnofsky performance status (KPS) and the use of chemotherapy had a significant impact on BRFS, and other factors, such as type of therapy (adjuvant *vs*. salvage), the total radiation dose and the use of hormonal therapy, did not influence BRFS (Table IV). In multivariate analysis, nPSA12 alone was an independent prognostic factor for BRFS after radiotherapy (Table V).

Table IV. *Univariate analysis of various potential prognostic factors for biochemical-free survival in patients with prostate cancer treated with postoperative radiotherapy.*

	Univariate analysis		
	n	BFS, 5-year rate (%)	*p*-Value
nPSA12 (ng/ml)			
<0.5	56	92.7%	**0.0002**
≥0.5	20	42.2%	
Therapy			
Adjuvant	42	81.9%	0.6615
Salvage	34	77.3%	
Surgical margin			
–	31	84.8%	0.2738
+	15	68.6%	
CAP			
–	15	92.9%	0.2497
+	34	75.2%	
SV			
–	30	88.4%	0.4448
+	14	75.0%	
Pathological T stage			
T0-2	62	100.0%	0.3445
T3-4	11	77.2%	
Pathological N stage			
N0	52	78.4%	0.6818
N1	7	71.4%	
Pelvic irradiation			
Yes	30	86.7%	0.3865
No	46	75.5%	
Age (years)			
<70	51	76.9%	0.2856
≥70	25	86.5%	
KPS (%)			
≤80	17	64.2%	**0.0239**
>80	58	84.6%	
Pre-treatment PSA (ng/ml)			
<20	40	72.5%	0.2022
≥20	29	85.0%	
Pre-radiotherapy PSA (ng/ml)			
<2	42	89.5%	**0.0160**
≥2	12	50.0%	
Gleason combined score			
≤6	24	95.8%	0.1315
>6	19	78.6%	
Differentiation			
Well/Moderate	49	79.0%	0.4524
Poor	22	82.6%	
T stage			
T0-2	62	100.0%	0.3445
T3-4	11	77.2%	
Use of chemotherapy			
Yes	11	45.5%	**0.0033**
No	62	86.6%	
Use of hormone therapy			
Yes	57	75.7%	0.1717
No	18	93.8%	
Use of postRT hormonetherapy			
Yes	40	73.8%	0.4407
No	26	82.0%	
Total radiation dose (Gy)			
<60	30	78.9%	0.7143
≥60	46	80.6%	

nPSA12, Nadir prostate-specific antigen within 12 months; KPS, Karnofsky performance status; BFS, biochemical-free survival; PSA, prostate-specific antigen.

Table V. *Multivariate analysis of various potential prognostic factors for biochemical-free survival in patients with prostate cancer treated with postoperative radiotherapy.*

	Multivariate analysis	
	RR (95% CI)	*p*-Value
nPSA12 (ng/ml)		
<0.5	7.403 (1.296-42.287)	**0.0244**
≥0.5		
KPS (%)		
≤80	2.156 (0.423-10.981)	0.3552
>80		
Pre-radiotherapy PSA (ng/ml)		
<2	2.107 (0.441-10.077)	0.3507
≥2		
Use of chemotherapy		
Yes	0.471 (0.061-3.608)	0.4685
No		

PSA, Prostate-specific antigen; KPS, Karnofsky performance status; RR, relative ratio; CI, confidence intervals.

Regarding clinical control, the median nPSA12s in patients without clinical failure after radiotherapy and those with clinical failure were 0.04 ng/ml (range, 0.00-5.90 ng/ml) and 0.90 ng/ml (range, 0.00-5.00 ng/ml), respectively. The 5-year actuarial PFS rates in patients with high nPSA12 levels and patients with low nPSA12 levels were 92.7% and 35.9%, respectively (Figure 5). The difference between these two groups was statistically significant ($p<0.0001$). In a univariate analysis, nPSA12, surgical margin status, KPS, pre-radiotherapy PSA and the use of chemotherapy had a statistically significant impact on PFS (Figure 5; Table VI). However, in a multivariate analysis, no factors were independent prognostic factors for PFS (Table VII).

Late morbidity of RTOG grade 2-3 was observed in 8 patients (11%). A total of 4 patients experienced late rectal toxicity and the remaining 4 patients had late urinary toxicity. There were no cases of grade 4 toxicity (Table VIII). Regarding 4 patients who suffered grade 3 late complications, CT-based treatment planning was carried out in only 1 patient (25%), and conformal therapy was supplemented in 1 patient (25%).

Discussion

The current study indicated that postoperative radiotherapy gave an excellent local control rate for patients treated with radical prostatectomy. Several reports have also indicated that postoperative radiotherapy gave an excellent local control rate for these tumors (11, 33-35). The EORTC trial reported the cumulative incidence of locoregional failure at 5 years of follow-up, and a statistically lower incidence of failure was seen

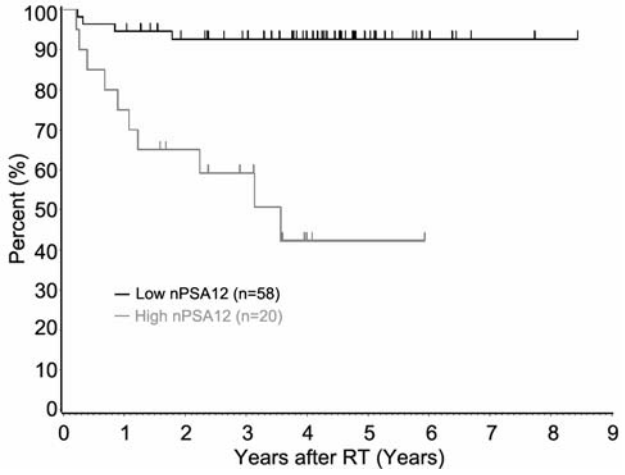

Figure 4. *Actuarial biochemical-free survival curves according to the level of nPSA12. There were significant differences in PFS between patients with a low nPSA12 value (<0.5 ng/ml) and those with a high nPSA12 value (≥0.5 ng/ml).*

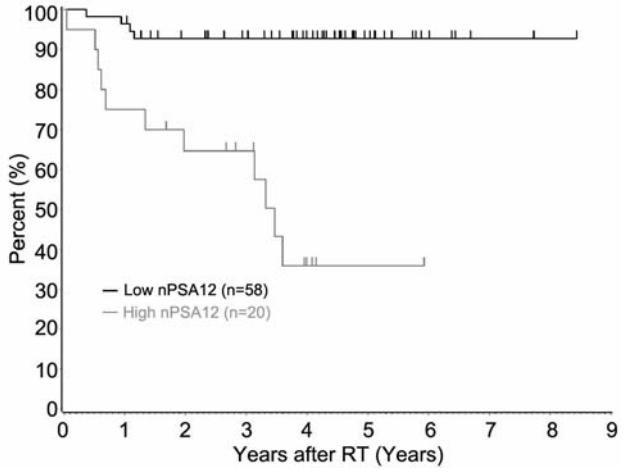

Figure 5. *Actuarial progression-free survival curves according to the level of nPSA12. There were significant differences in PFS between patients with a low nPSA12 value (<0.5 ng/ml) and those with a high nPSA12 value (≥0.5 ng/ml).*

in the adjuvant radiotherapy arm (5.4%) than in the observation arm (15.4%) (11). Cozzarini *et al*. retrospectively analyzed 237 patients who underwent postoperative radiotherapy (within 6 months of surgery), and indicated that the actuarial 8-year local control rate was 93% (33). In the current study, only 5 out of 76 patients (7%) developed local failure after radiotherapy.

Although the dose response in patients who undergo postoperative radiotherapy for localized prostate cancer has not yet been clearly established, higher doses with curative intent can result in favorable outcomes in some patients. In the current study, the 5-year local control in 76 patients treated with a median dose of 60 Gy was 92.2%, and 22 out of 22 patients (100%) treated with 66 Gy or more had achieved local control. Several reports have suggested that radiation doses of 65 Gy or more are associated with improved biochemical PFS (36, 37). Therefore, radiation doses of 65 Gy or more appear to be appropriate for prostate cancer patients when treated with postoperative radiotherapy. However, in the current study, it is important to note that the almost all patients who suffered grade 3 late complications were treated without CT-based treatment planning and/or conformal therapy. Therefore, CT-based treatment planning and/or conformal therapy should be required to reduce the late complications. Concerning the radiation field, we did not find significant differences in local control between patients treated for the whole pelvis with or without boost and those treated with a localized field only. Therefore, localized field irradiation may be sufficient in this patient population. Further studies are required to determine whether a localized field is sufficient for these patients.

The current study also indicated that patients with a high nPSA12 had a significantly lower BRFS rate than patients with a low nPSA12, and nPSA12 was an independent prognostic factor for BRFS in patients with localized prostate cancer treated with postoperative radiotherapy. Moreover, patients with low nPSA12 levels had significantly higher PFS than those with high nPSA12 level, although nPSA12 was not an independent prognostic factor for PFS in the multivariate analysis. To our knowledge, this is the first report to demonstrate the utility of nPSA12 in determining prognosis in patients with localized prostate cancer treated with postoperative radiotherapy. Concerning previously untreated prostate cancer, Alcantara *et al*. indicate that nPSA12 is independent of radiation dose, T stage, Gleason score, pretreatment initial PSA, age and PSA doubling time, and dichotomized nPSA12 (≤2 *versus* >2 ng/ml) was independently related to distant metastasis and cause-specific mortality (15). Ray *et al*. indicated that patients with nPSA12 ≤2.0 ng/ml had significantly higher 8-year PSA failure-free survival and overall survival than patients with nPSA12 >2.0 ng/ml, and nPSA12 was an independent prognostic factor for prostate cancer patients treated with radiotherapy alone (16). Furthermore, Ogawa *et al*. indicated that nPSA12 was an independent prognostic factor for hormone-refractory prostate cancer patients treated with radiotherapy (38). These results suggest that nPSA12 may be a useful marker for patients with localized prostate cancer treated with postoperative radiotherapy as well as patients with previously untreated prostate cancer treated with radiotherapy and clinically localized hormone-refractory prostate cancer.

Several previous studies have suggested other potential factors associated with the risk of prostate cancer recurrence, such as pre-radiotherapy PSA, PSA velocity and PSA doubling time (PSADT) (9, 39-42). For patients treated with salvage radiotherapy, Gleason score, pre-radiotherapy PSA level, surgical margins, PSADT and seminal vesicle invasion are

Table VI. *Univariate analysis of various potential prognostic factors for progression-free survival in patients with prostate cancer treated with postoperative radiotherapy.*

	Univariate analysis		
	n	PFS, 5-year rate (%)	*p*-Value
nPSA12 (ng/ml)			
<0.5	56	92.7%	**<0.0001**
≥0.5	20	35.9%	
Therapy			
Adjuvant	42	72.7%	0.1838
Salvage	34	69.8%	
Surgical margin			
–	31	96.8%	**0.0258**
+	15	56.7%	
CAP			
–	15	86.7%	0.7355
+	34	77.6%	
SV			
–	30	93.3%	0.0997
+	14	68.8%	
Pathological T stage			
T0-2	62	90.9%	0.4793
T3-4	11	78.5%	
Pathological N stage			
N0	52	76.6%	0.8399
N1	7	71.4%	
Pelvic irradiation			
Yes	30	76.5%	0.9782
No	46	78.7%	
Age (years)			
<70	51	73.3%	0.2382
≥70	25	87.0%	
KPS (%)			
≤80	17	57.3%	**0.0417**
>80	58	82.8%	
Pre-treatment PSA (ng/ml)			
<20	40	74.8%	0.6650
≥20	29	82.6%	
Pre-radiotherapy PSA (ng/ml)			
<2	42	90.4%	**0.0103**
≥2	12	44.4%	
Gleason combined score			
≤6	24	95.8%	0.0706
>6	19	71.8%	
Differentiation			
Well/Moderate	49	85.3%	0.0744
Poor	22	65.4%	
Use of chemotherapy			
Yes	11	45.5%	**0.0102**
No	62	83.8%	
Use of hormonetherapy			
Yes	57	75.6%	0.3841
No	18	82.6%	
Use of postRT hormone therapy			
Yes	40	73.1%	0.5473
No	26	84.6%	
Total radiation dose (Gy)			
<60	30	72.7%	0.6112
≥60	46	81.2%	

nPSA12, Nadir prostate-specific antigen within 12 months; KPS, Karnofsky performance status; PSA, prostate-specific antigen; PFS, progression-free survival.

Table VII. *Multivariate analysis of various potential prognostic factors for progression-free survival in patients with prostate cancer treated with postoperative radiotherapy.*

	Multivariate analysis	
	RR (95% CI)	*p*-Value
nPSA12 (ng/ml)		
<0.5	5.183 (0.326-82.512)	0.2439
≥0.5		
Surgical margin		
–	12.683 (0.656-245.321)	0.0928
+		
KPS (%)		
≤80	10.998 (0.426-283.891)	0.1483
>80		
Pre-radiotherapy PSA (ng/ml)		
<2	0.255 (0.010-6.570)	0.4094
≥2		
Use of chemotherapy		
Yes	0.174 (0.007-4.082)	0.2771
No		

PSA, Prostate-specific antigen; KPS, Karnofsky performance status; RR, relative ratio; CI, confidence intervals.

Table VIII. *Late complications in patients with prostate cancer treated with postoperative radiotherapy.*

	Toxicity grade		Total dose (Grade 3)
	Grade 2	Grade 3	
Rectal			
Bleeding	3	1	67.8 Gy
Urinary			
Ureteral obstruction	1	0	
Incontinence	0	2	60 Gy
Incontinence + Structure	0	1	56.6 Gy

prognostic variables for a durable response to salvage radiotherapy (41). Sasaki *et al*. indicated that a low pre-radiotherapy PSA level is a significant predictor of biochemical control for postoperative radiotherapy in patients with prostate cancer (42). King *et al*. reported that postoperative PSA velocity independently predicts for the failure of salvage radiotherapy after radical prostatectomy (39). Numata *et al*. indicated that PSADT appears to be a good predictor of response to salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy (9).

Concerning the timing of radiotherapy, adjuvant radiotherapy following radical prostatectomy has been compared to salvage therapy in numerous retrospective studies that have included patients with high-risk pathological features (10, 43-45). Overall, the results from those studies support the

use of adjuvant radiotherapy, with demonstrated improvements in local and biochemical control. In the current study, there was no significant difference in biochemical control between the adjuvant radiotherapy group and the salvage radiotherapy group. One of the reasons may be the small number of patients in the current study. Our results also indicated that pre-radiotherapy PSA, KPS and the use of chemotherapy had a significant impact on BRFS, although multivariate analyses failed to confirm the significance. Further studies are required to evaluate the influence of additional factors, such as PSA velocity and PSADT, on clinical outcomes for localized hormone-refractory patients treated with radiotherapy.

In conclusion, our results indicated that postoperative radiotherapy gave an excellent local control rate for localized prostate cancer after radical prostatectomy, and should be considered the treatment of choice for these tumors. Our results also indicated that nPSA12 is an early predictor of biochemical failure that is independent of radiotherapy dose and other determinants of outcome after postoperative radiotherapy for prostate cancer patients treated with radical prostatectomy. Therefore, nPSA12 could potentially help identify patients at high risk who might benefit from the earlier application of systemic therapy. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

Acknowledgements

Supported by Grants-in-Aid for Cancer Research (Grant Nos. 10-17 and 14-6) from the Ministry of Health, Labor and Welfare of Japan. We thank all radiation oncologists who participated in this study throughout Japan. Their efforts to provide information to us make these surveys possible. We are grateful for the continuous thoughtful support we have received from the U.S. PCS committee for over 10 years.

References

1 Van der Kwast TH, Bolla M, Van Poppel H, Van Cangh P, Vekemans K, Da Pozzo L, Bosset JF, Kurth KH, Schröder FH and Collette L; EORTC 22911: Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J Clin Oncol *25*: 4178-4186, 2007.

2 Kupelian P, Katcher J, Levin H, Zippe C and Klein E: Correlation of clinical and pathologic factors with rising prostate-specific antigen profiles after radical prostatectomy alone for clinically localized prostate cancer. Urology *48*: 249-260, 1996.

3 Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP and Barrett DM: Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol *152*: 1850-1857, 1994.

4 Catalona WJ and Smith DS: Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. J Urol *160*: 2428-2434, 1998.

5 Walsh PC, Partin AW and Epstein JI: Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. J Urol *152*: 1831-1836, 1994.

6 Gerber GS, Thisted RA, Scardino PT, Frohmuller HG, Schroeder FH, Paulson DF, Middleton AW Jr, Rukstalis DB, Smith JA Jr, Schellhammer PF, Ohori M, Chodak GW: Results of radical prostatectomy in men with clinically localized prostate cancer. JAMA *276*: 615-619, 1996.

7 Wheeler TM, Dillioglugil O, Kattan MW, Arakawa A, Soh S, Suyama K, Ohori M and Scardino PT: Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. Hum Pathol *29*: 856-862, 1998.

8 Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, Slawin K and Scardino PT: Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol *174*: 903-907, 2005.

9 Numata K, Azuma K, Hashine K and Sumiyoshi Y: Predictor of response to salvage radiotherapy in patients with PSA recurrence after radical prostatectomy: the usefulness of PSA doubling time. Jpn J Clin Oncol *35*: 256-259, 2005.

10 Morgan SC, Waldron TS, Eapen L, Mayhew LA, Winquist E, Lukka H and Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care: Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: a systematic review and meta-analysis. Radiother Oncol *88*: 1-9, 2008.

11 Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Maréchal JM, Scalliet P, Haustermans K, Piérart M and European Organization for Research and Treatment of Cancer: Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet *366*: 572-578, 2005.

12 Vargas C, Kestin LL, Weed DW, Krauss D, Vicini FA and Martinez AA: Improved biochemical outcome with adjuvant radiotherapy after radical prostatectomy for prostate cancer with poor pathologic features. Int J Radiat Oncol Biol Phys *61*: 714-724, 2005.

13 National Comprehensive Cancer Network: NCCN clinical practice guidelines in oncologyTM. Prostate cancer. V.2. 2009. http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf.

14 Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E and Crawford ED: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA *296*: 2329-2335, 2006.

15 Alcantara P, Hanlon A, Buyyounouski MK, Horwitz EM and Pollack A: Prostate-specific antigen nadir within 12 months of prostate cancer radiotherapy predicts metastasis and death. Cancer *109*: 41-47, 2007.

16 Ray ME, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Zelefsky MJ, Zietman AL and Kuban DA: Nadir prostate-specific antigen within 12 months after radiotherapy predicts biochemical and distant failure. Urology *68*: 1257-1262, 2006.

17 Zietman AL, Tibbs MK, Dallow KC, Smith CT, Althausen AF, Zlotecki RA and Shipley WU: Use of PSA nadir to predict subsequent biochemical outcome following external beam radiation therapy for T1-2 adenocarcinoma of the prostate. Radiother Oncol *40*: 159-162, 1996.

18 Lee WR, Hanlon AL and Hanks GE: Prostate-specific antigen nadir following external beam radiation therapy for clinically localized prostate cancer: the relationship between nadir level and disease-free survival. J Urol *156*: 450-453, 1996.

19 Crook JM, Bahadur YA, Bociek RG, Perry GA, Robertson SJ and Esche BA: Radiotherapy for localized prostate carcinoma. The correlation of pretreatment prostate-specific antigen and nadir prostate-specific antigen with outcome as assessed by systematic biopsy and serum prostate specific antigen. Cancer *79*: 328-336, 1997.

20 Ray ME, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Shipley WU, Zelefsky MJ, Zietman AL and Kuban DA: PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: a multi-institutional analysis. Int J Radiat Oncol Biol Phys *64*: 1140-1150, 2006.

21 Hanlon AL, Diratzouian H and Hanks GE: Posttreatment prostate-specific antigen nadir highly predictive of distant failure and death from prostate cancer. Int J Radiat Oncol Biol Phys *53*: 297-303, 2002.

22 Pollack A, Hanlon AL, Movsas B, Hanks GE, Uzzo R and Horwitz EM: Biochemical failure as a determinant of distant metastasis and death in prostate cancer treated with radiotherapy. Int J Radiat Oncol Biol Phys *57*: 19-23, 2003.

23 Teshima T and Japanes PCS Working Group: Patterns of care study in Japan: Jpn J Clin Oncol *35*: 497-506, 2005.

24 Sasaki T, Nakamura K, Ogawa K, Onishi H, Otani Y, Koizumi M, Shioyama Y, Teshima T and Japanese Patterns of Care Study Working Subgroup of Prostate Cancer: Postoperative radiotherapy for patients with prostate cancer in Japan; Changing trends in national practice between 1996-98 and 1999-2001: Patterns of care study for prostate cancer. Jpn J Clin Oncol *36*: 649-654, 2006.

25 Hanks GE, Coia LR and Curry J: Patterns of care studies: past, present and future. Semin Radiat Oncol *7*: 97-100, 1997.

26 Owen JB, Sedransk J and Pajak TF: National averages for process and outcome in radiation oncology: Methodology of the patterns of care study. Semin Radiat Oncol *7*: 101-107, 1997.

27 Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH and Sandler H: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys *65*: 965-974, 2006.

28 SAS procedure reference, version 6. 1st ed. Tokyo: SAS Institute Iin Japan; 1995.

29 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

30 Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep *50*: 163-170, 1966.

31 Cox DR: Regression models and life tables. J R Stat Soc *34*: 187-220, 1972.

32 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31*: 1341-1346, 1995.

33 Cozzarini C, Bolognesi A, Ceresoli GL, Fiorino C, Rossa A, Bertini R, Colombo R, Da Pozzo L, Montorsi F, Roscigno M, Calandrino R, Rigatti P and Villa E: Role of postoperative radiotherapy after pelvic lymphadenectomy and radical retropubic prostatectomy: a single institute experience of 415 patients. Int J Radiat Oncol Biol Phys *59*: 674-683, 2004.

34 Petrovich Z, Lieskovsky G, Langholz B, Jozsef G, Streeter OE Jr and Skinner DG: Postoperative radiotherapy in 423 patients with pT3N0 prostate cancer. Int J Radiat Oncol Biol Phys *53*: 600-609, 2002.

35 Choo R, Hruby G, Hong J, Hong E, DeBoer G, Danjoux C, Morton G, Klotz L, Bhak E and Flavin A: Positive resection margin and/or pathologic T3 adenocarcinoma of prostate with undetectable postoperative prostate-specific antigen after radical prostatectomy: to irradiate or not? Int J Radiat Oncol Biol Phys *52*: 674-680, 2002.

36 Macdonald OK, Schild SE, Vora SA, Andrews PE, Ferrigni RG, Novicki DE, Swanson SK and Wong WW: Radiotherapy for men with isolated increase in serum prostate-specific antigen after radical prostatectomy. J Urol *170*: 1833-1837, 2003.

37 Anscher MS, Clough R and Dodge R: Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. Int J Radiat Oncol Biol Phys *48*: 369-375, 2000.

38 Ogawa K, Nakamura K, Sasaki T, Onishi H, Koizumi M, Shioyama Y, Araya M, Mukumoto N, Mitsumori M and Teshima T: External beam radiotherapy for clinically localized hormone-refractory prostate cancer: Clinical Significance of Nadir Prostate-Specific Antigen value within 12 Months. Int J Radiat Oncol Biol Phys *74*: 759-765, 2009.

39 King CR, Presti JC, Brooks JD, Gill H and Spiotto MT: Postoperative prostate-specific antigen velocity independently predicts for failure of salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys *70*: 1472-1477, 2008.

40 Wadasaki K, Kaneyasu Y, Kenjo M, Matsuura K, Murakami Y, Hashimoto Y, Ito K, Kiriu H and Ito A: Treatment results of adjuvant radiotherapy and salvage radiotherapy after radical prostatectomy for prostate cancer. Int J Clin Oncol *12*: 37-41, 2007.

41 Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, Klein EA, Kupelian PA, Roehrborn CG, Pistenmaa DA, Pacholke HD, Liauw SL, Katz MS, Leibel SA, Scardino PT and Slawin KM: Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA *291*: 1325-1332, 2004.

42 Sasaki T, Nakamura K, Shioyama Y, Ohga S, Toba T, Urashima Y, Yoshitake T, Terashima H, Koga H, Naito S, Noma H, Komatsu K, Yamaguchi A, Hiratsuka Y, Hirano T, Hanada K, Abe M, Fujisawa Y and Honda H: Low pre-radiotherapy prostate-specific antigen level is a significant predictor of treatment success for postoperative radiotherapy in patients with prostate cancer. Anticancer Res *26*: 2367-2374, 2006.

43 Schild SE, Wong WW, Grado GL, Halyard MY, Novicki DE, Swanson SK, Larson TR and Ferrigni RG: The result of radical retropubic prostatectomy and adjuvant therapy for pathologic stage C prostate cancer. Int J Radiat Oncol Biol Phys *34*: 535-541, 1996.

44 Morris MM, Dallow KC, Zietman AL, Park J, Althausen A, Heney NM and Shipley WU: Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys *38*: 731-736, 1997.

45 Valicenti RK, Gomella LG, Ismail M, Strup SE, Mulholland SG, Dicker AP, Petersen RO and Newschaffer CJ: The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: a matched-pair analysis. Int J Radiat Oncol Biol Phys *45*: 53-58, 1999.

Received May 6, 2009
Revised July 22, 2009
Accepted September 2, 2009