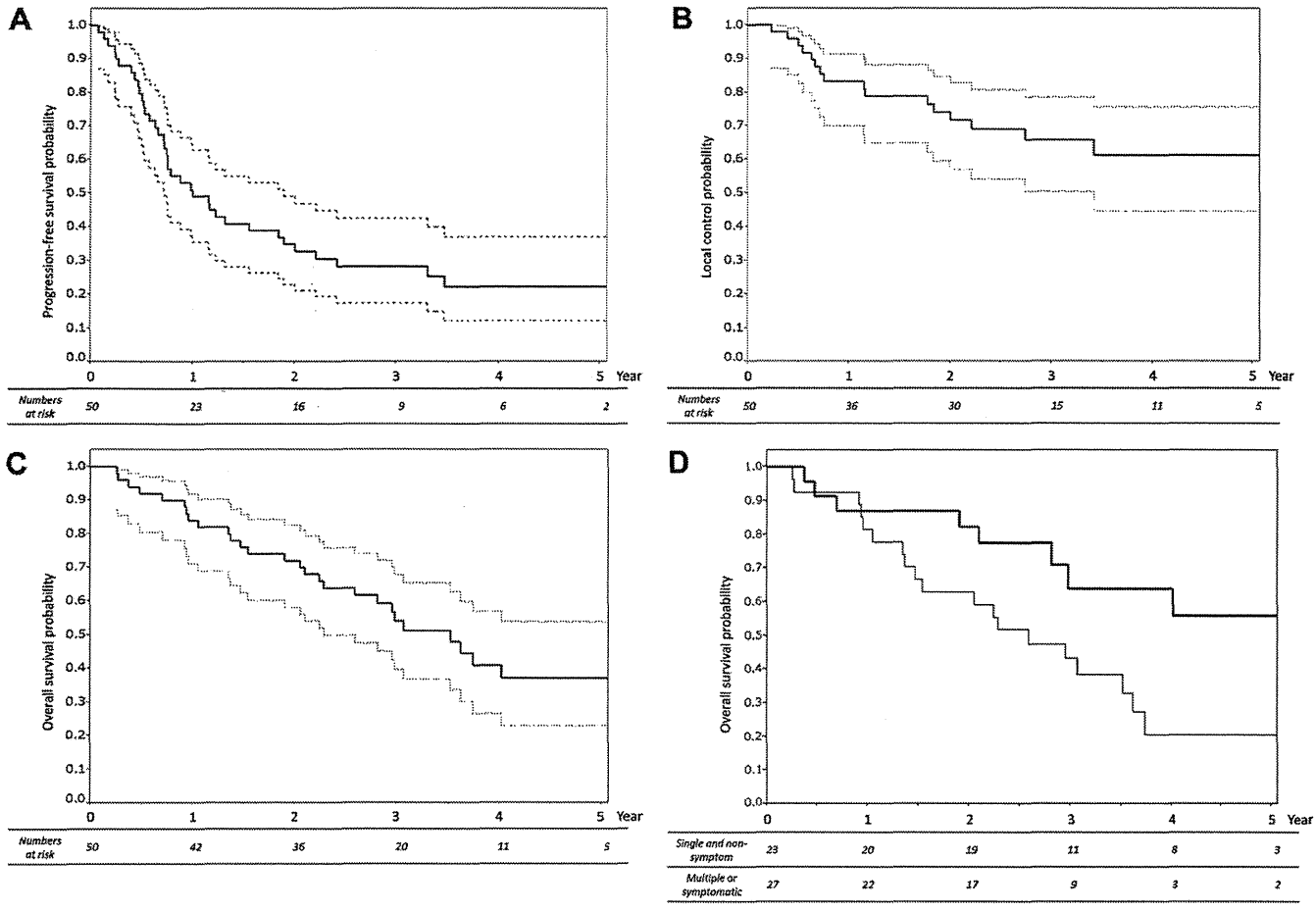

FIGURE 3. Plots of the progression-free survival (*A*), local control (*B*), and overall survival (*C*) probabilities with 95% confidence intervals (dash lines) among patients who received radiotherapy for thoracic lymph node recurrence after surgery. Plots of the overall survival (*D*) probabilities in the patients who were both nonsymptomatic and with single involved lymph nodes station ($n = 23$, bold line) and the patients who were symptomatic or with multiple involved lymph nodes stations ($n = 27$, faint line).

lymph nodes station. The overall survival probability of those patients and the remaining patients are shown in Figure 3*D*. The initial sites of the disease progression were not associated with these factors. The use of concurrent chemotherapy did not affect the overall or progression-free survival. There were five patients who had single-station lymph node recurrence in the supraclavicular area. Two of these patients survived more than 3 years after radiotherapy without any other disease recurrences.

Treatment Compliance and Toxicity

The planned total radiotherapy dose was delivered to 49 patients (98%) of 50 patients. One patient (2%) developed grade 2 pneumonitis and esophagitis at 56 Gy/60 Gy and refused further therapy. The remaining patients showed acute toxicity of grade 2 in six patients (12%) (esophagitis, pneumonitis, malaise, and arthralgia), acute toxicity of grade 3 in one patient (2%; dyspnea), and late toxicity of grade 3 in one patients (2%; pneumonitis). Grade 3 toxicities were observed in patients receiving regional nodal radiotherapy.

Overall Survival of the Patients Who Did Not Receive Radiotherapy

The overall probability of survival of the patients who did not receive radiotherapy is shown in Figure 4. The median survival was 443 days, and the 1-year and the 3-year survival probabilities were 58.8% and 5.9%, respectively.

DISCUSSION

Many of the patients who undergo radical resection for NSCLC develop recurrence with a dismal prognosis. The use of chemotherapy is generally recognized as a standard option to provide objective responses and small improvement in survival for patients with recurrent disease just as performed for initial stage IV patients.

Postoperative lymph node recurrence is common but it mostly occurs along with distant metastases.[4] Systemic therapy would be indicated for patients with recurrences in both lymph nodes and a distant organ. However, the disease is considered to be localized if thoracic lymph nodes are involved but no other metastasis is observed after systematic workup,

TABLE 3. Initial Site of Disease Progression after Radiotherapy

Site	Number of Patients
Pulmonary metastasis or pleural dissemination	11
Extrathoracic distant metastasis	7
Lymph nodes out of the radiation field	9
Lymph nodes within the radiation field	9
Alive without the disease	14

TABLE 4. Multivariate Analysis of Overall Survival after Radiotherapy

Variable	Reference	HR	95% CI	*p*
Symptom	Absent	3.86	1.72–8.57	0.0014
Number of stations	Single	2.70	1.21–6.12	0.0152

Cox proportional hazard model.
HR, hazard ratio; CI, confidence interval.

and these patients may have a chance to be cured. A report of the anatomic location of NSCLC recurrences in 378 patients showed that there were 30 mediastinal lymph node recurrences (7.9%).[6] Curative intent radiotherapy can be indicated for this specific state of the disease. The database of this institution yielded 50 patients who underwent thoracic radiotherapy in this setting, and the short- and the long-term outcomes of this treatment were analyzed. The treatment was completed in most of the patients and no serious complications were recorded. The median overall survival was 37 months and the 5-year survival rate was 36.1%. Ten (20%) of 50 patients were alive longer than 3 years without any additional recurrence after the radiotherapy. These results suggest that a subset of patients with postoperative lymph node recurrence may be cured or enjoy a long-lasting progression-free survival by thoracic radiotherapy.

To date there have been few reports that summarize the treatments for recurrent disease in the literature.[1–3,7] Previous reports show that the median postrecurrent survival ranges from 8.1 to 18.7 months. Limiting the results to the patients who underwent radiotherapy for lymph node recurrence or other locoregional recurrence shows a median survival after recurrence of 14 to 15 months.[5,8–10]

The CEA values were used for monitoring the treatment effects in this study. The normal CEA values were required for the CR definition after radiotherapy, although the use of CEA in NSCLC remains controversial. Several reports have indicated that elevated serum CEA levels are associated with an unfavorable prognosis and occult lymph node metastasis in NSCLC patients.[11,12] Indeed, we observed several patients whose lymph nodes shrank to normal size by radiotherapy but their CEA levels were still elevated comparing with the normal limit. By using the size criteria only, we might overestimate the CR rate.

The outcomes in the current study were favorable as a treatment for recurrent disease. The CR rate was as high as 65%. The median survival and the 5-year survival rate in the present series were considerably longer than those of previous reports.[5,8–10] This is partially because of significant improvements in conformal radiotherapy within the past one or two decades, which have enabled the use of intensive radiotherapy to treat recurrent disease with less radiation toxicity. Another reason may exist in the differences in patient backgrounds. More patients with associated symptoms were included and the size of the recurrent tumor was larger in the previous studies. In contrast, the disease was nonsymptomatic, the involved lymph nodes were localized in only one station, and the size of the target tumor was smaller than 30 mm in many of the patients in this study.

The prognostic impact of variables was evaluated by univariate and multivariate analyses to select the patients who may benefit most from this treatment. The analysis revealed

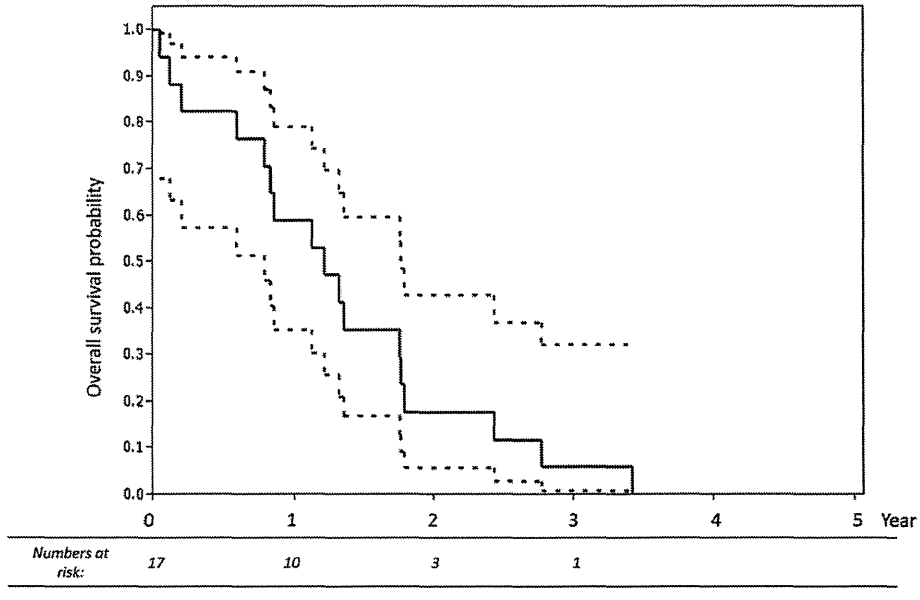

FIGURE 4. Plots of the overall survival probabilities with 95% confidence intervals (dash lines) among patients who did not receive radiotherapy ($n = 17$).

that absence of symptoms at the time of recurrence and a single involved lymph node station were favorable prognostic indicators after recurrence. Interestingly, both prognostic factors in this study were associated with early presentation of recurrence. The surveillance program in this institution, which includes chest CT one or two times a year is relatively intensive in comparison with the guideline-recommended programs.[13] PET scan was also useful, because PET distinguished thoracic lymph node recurrence from nonspecific postoperative change. The intensive surveillance using chest CT and PET may play an important role in the early diagnosis of lymph node recurrence. The results of the present study and the comparisons with previous studies suggest that early detection of recurrence after surgery may contribute to achieving good disease control after radiation and, as a result, longer survival.

A favorable local control rate within the irradiated field was obtained by thoracic radiotherapy without any severe adverse events. The radiation dose prescribed in this study was considered to be adequate. Radiotherapeutic approaches in this study were classified into regional nodal irradiation and involved-field irradiation. Regional nodal radiation therapy covers a larger field and, as a result, may allow more irradiation to adjacent organs such as lung and esophagus, in comparison with involved-field radiation, which targets only metastatic nodes. Local recurrence-free survival or patterns of failure after radiotherapy were not associated with the choice of the radiation approach. On the basis of this result, restricting the target volume to the involved nodal regions might be an option as a radiation approach for thoracic lymph node recurrence. These phenomena were similarly observed in the comparison between elective nodal irradiation and involved-field irradiation for locally advanced unresectable NSCLC.[14,15]

Systemic chemotherapy is a mainstay of treatment for recurrent NSCLC. Only a small number of patients received concurrent chemotherapy in this study. Considering that concurrent chemoradiotherapy is a standard treatment for the patients with inoperable stage III NSCLC, this approach can be another option for regional lymph node recurrence after surgery. When selecting the treatment strategy for patients with thoracic lymph node metastases, it should be noted that there were essential differences between stage III NSCLC and postoperative recurrences. First, the primary tumor had been resected in postoperative patients. Second, the nodal disease was observed after at least a few months of disease-free status. In addition, the sizes of involved lymph nodes were relatively small and their distribution was limited to a couple of stations in most of the recurrent patients. Therefore, thoracic lymph node recurrences were considered to be local disease, and curative intent radiation therapy was the treatment of choice. In contrast, the involved lymph nodes in inoperable stage III patients are usually bulky and extended to multiple nodal stations. Consequently, the prognostic advantage was not observed in the patients who received concurrent chemotherapy. However, because distant metastasis or pleural dissemination was the initial site of the disease progression in 18 patients (36%), the use of chemotherapy may thus have additional effects on controlling the subclinical systemic disease.

The strength of this study is that as a single-institutional study it provided complete information on the clinical course after surgery including recurrence, failure after radiotherapy, final outcomes, well-controlled planning, and quality of radiotherapy.

There are limitations that need to be acknowledged. This study may include the patients whose involved lymph nodes were relatively limited in terms of their number and their location. Because this retrospective analysis was inherently affected by a selection bias associated with the use of radiotherapy, a straightforward comparison between the patients who received radiotherapy and the patients who did not receive radiotherapy was not allowed. Therefore, the real possible benefits of radiotherapy for thoracic lymph node recurrence over chemotherapy alone remain uncertain. Another limitation, as in other studies of nonsurgical therapies, is the lack of a pathological diagnosis. Lymph node sampling under mediastinoscopy or thoracotomy is usually impossible or is a high-risk procedure because systematic mediastinal lymph node dissection is generally performed during the initial surgery. Accurate targeting of an involved lymph node by endobronchial ultrasound-guided transbronchial needle aspiration requires technical skills and experience because the anatomy in the mediastinum was affected by surgery. FDG-PET was used to make a diagnosis in 31 of 40 patients without pathological evidence; however, it was not available in the remaining nine patients. Even though FDG-PET shows good diagnostic performance in detecting recurrence in postoperative NSCLC patients with a fairly high sensitivity (97%) and specificity (96%) as seen in our previous report,[16] we could not eliminate the possibility of false-positive diagnoses in our study. In addition, the sample size of this study was relatively small because this type of recurrence is uncommon. Despite these essential shortcomings, the data demonstrated the favorable results of radiotherapy for patients whose characteristics were described in this study.

In conclusion, radiation therapy for thoracic lymph node recurrence after complete resection is safe and provides acceptable disease control. This treatment provides better outcomes if the disease is asymptomatic and has a single-station involvement. Early detection of thoracic lymph node recurrence may therefore improve the effectiveness of this treatment strategy.

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Effects of interportal error on dose distribution in patients undergoing breath-holding intensity-modulated radiotherapy for pancreatic cancer: evaluation of a new treatment planning method

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In patients with pancreatic cancer, intensity-modulated radiotherapy (IMRT) under breath holding facilitates concentration of the radiation dose in the tumor, while sparing the neighboring organs at risk and minimizing interplay effects between movement of the multileaf collimator and motion of the internal structures. Although the breath-holding technique provides high interportal reproducibility of target position, dosimetric errors caused by interportal breath-holding positional error have not been reported. Here, we investigated the effects of interportal breath-holding positional errors on IMRT dose distribution by incorporating interportal positional error into the original treatment plan, using random numbers in ten patients treated for pancreatic cancer. We also developed a treatment planning technique that shortens breath-holding time without increasing dosimetric quality assurance workload. The key feature of our proposed method is performance of dose calculation using the same optimized fluence map as the original plan, after dose per fraction in the original plan was cut in half and the number of fractions was doubled. Results confirmed that interportal error had a negligible effect on dose distribution over multiple fractions. Variations in the homogeneity index and the dose delivered to 98%, 2%, and 50% of the volume for the planning target volume, and the dose delivered to 1 cc of the volume for the duodenum and stomach were ± 1%, on average, in comparison with the original plan. The new treatment planning method decreased breath-holding time by 33%, and differences in dose-volume metrics between the original and the new treatment plans were within ± 1%. An additional advantage of our proposed method is that interportal errors can be better averaged out; thus, dose distribution in the proposed method may be closer to the planned dose distribution than with the original plans.

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Key words: IMRT, pancreas cancer, breath-holding technique

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I. INTRODUCTION

Pancreatic cancer is currently the fifth-leading cause of death from cancer in Japan.[1] The number of people dying from this cancer has increased annually, and reached approximately 28,000 deaths in 2010. Although the first-choice curative treatment for pancreatic cancer remains surgery, more than 80% of patients have nonresectable disease at the time of diagnosis.[2] These cases are often treated with chemoradiotherapy, but the presence of radiosensitive organs at risk (OARs) around the pancreas, including the duodenum and stomach, prevents the delivery of a sufficient radiation dose, which may result in unfavorable outcomes.[3-9] Thus, an important issue in the treatment of pancreatic cancer generally is how to deliver a more intense radiation dose.

Intensity-modulated radiotherapy (IMRT) facilitates the concentration of radiation dose in the tumor, while sparing doses to OARs, and can therefore reduce the rate of gastrointestinal toxicity.[10-12] Respiratory motion remains an obstacle to dose delivery, however, and pancreatic tumor motion has been confirmed to be greater than 10 mm using several modalities.[13] When respiratory motion is not managed, a larger internal margin is required to fully cover geometric changes in free breathing,[14] which, in turn, results in the incorporation of a large volume of OARs into the planning target volume (PTV) and the possibility of severe gastrointestinal toxicity.[15] Additionally, the dosimetric advantage of IMRT is degraded significantly by interplay between movement of the multileaf collimator (MLC) and motion of the internal structures,[16-18] resulting in unintended underdose to the tumor and/or overdose to normal tissues. These problems seriously hamper the widespread adoption of IMRT for moving tumors, and accordingly indicate the need for respiratory management.

Our department is currently conducting a phase I/II radiation dose escalation study of full-dose gemcitabine with IMRT in pancreatic cancer patients under end-exhalation breath-holding (EE-BH) conditions with a visual-feedback technique (BH-IMRT).[16-18] The goal is to evaluate the possible impact of our protocol on response, toxicity, pain relief, and outcome in patients with locally advanced nonresectable pancreatic cancer, with reference to previous dose escalation trials of full-dose gemcitabine with conventional RT at the University of Michigan.[9,19] We reported previously that the EE-BH technique provided high interportal reproducibility of target position in pancreatic cancer.[20] However, the effects of interportal BH positional error on dosimetric errors have not been reported before. Our previous study also showed that a minimum BH time of 15 sec was required at the lowest dose level (2.6 Gy per fraction) at a dose rate of 600 monitor units (MU)/min. MUs per port were increased at the higher prescription dose levels in dose-escalation studies. A long BH time of > 15 sec at EE is typically not only difficult even for healthy people, but also has the potential to cause dosimetric error between the planned and delivered dose distribution as a result of baseline drift.[21] Generally, MUs per port can be reduced in multiport plans having different gantry and couch angles, but dosimetric quality assurance (DQA) of multiport plans requires measurement of each port and is, thus, laborious and time consuming.

The purpose of the present study was to investigate the effects of interportal BH positional errors on dose distribution, and to propose a treatment planning technique that both reduces the effect of interportal BH positional errors and shortens BH time without increasing DQA workload.

II. MATERIALS AND METHODS

This study was conducted in ten patients who underwent BH-IMRT for pancreatic cancer at Kyoto University Hospital between May 2010 and June 2011. Clinical target volume (CTV) and OARs, including duodenum, stomach, kidney, liver, spleen, and spinal cord, were delineated manually by a single radiation oncologist to eliminate interobserver variation. A PTV was created by adding isotropic margins of 5 mm to the CTV. The dynamic IMRT plan was

designed using Eclipse (Helios, ver. 8.6.15; Varian Medical Systems, Palo Alto, CA). Five fixed coplanar ports with gantry angles of 40°, 100°, 180°, 260°, and 320° were selected. The prescribed dose was 39 to 45 Gy in 15 fractions, with beam energy and dose rate of 15 MV photon beam and 600 MU/min, respectively. The treatment plan for the planning CT was used as the original treatment plan in the present study. The specification and technical details of CT data acquisition and dose constraints have been reported elsewhere.[20-22]

A. Effects of interportal breath-hold positional error on dose distribution

To incorporate interportal positional error into the treatment plan, a total of 750 sets of ten patients × five ports × 15 fractions, including LR, AP, and SI coordinates of random numbers were generated according to a normal distribution. Means and standard deviations (SDs) of the normal distribution were based on the results of our previous study.[20] Each of the calculated random numbers was assigned to the isocenter position for each port, and doses were then recalculated under the same MUs and an identical beam setup. Variations in homogeneity index (HI) and the dose delivered to 98% ($D_{98\%}$), 2% ($D_{2\%}$), and 50% ($D_{50\%}$) of the volume for PTV, and the dose delivered to 1 cc of the volume (D_{1cc}) for the duodenum and stomach were evaluated in comparison with the original plan. HI was calculated in accordance with the definition in ICRU report 83.[23]

B. Treatment planning to shorten the breath-hold time

To shorten the BH time without complicating the DQA procedure, we propose a new treatment plan called the double-exposure half-dose plan (DEHD plan). First, the dose per fraction of the original plan was cut in half and the number of fractions was doubled, and leaf motion sequence was then determined using the same optimized fluence map as in the original plan. If this step is skipped, leaf motion speed is doubled, which results in the delay of MLC motion, due to exceeding the maximum leaf speed.[24,25] Finally, the dose calculation was performed using newly created fluence maps. A flow chart for the procedure of the DEHD plan is shown in Fig. 1. The validity of this method was assessed by evaluating HI, $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ for the PTV, and D_{1cc} for the stomach and duodenum.

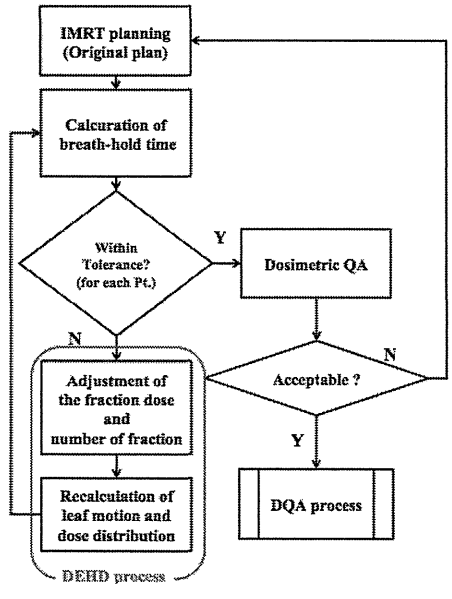

FIG. 1. Flow chart of the DEHD planning procedure.

C. Comparison of calculated dose fluence maps

To verify the DEHD plan, the dose distributions for each port in the DEHD plan were calculated on a plane perpendicular to the radiation field at a depth of 10 cm with a virtual phantom on Eclipse, and were then compared with those in the original plan using commercially available radiation dosimetry software (DD system, ver. 9.4; R-Tech Inc., Tokyo, Japan). The dose distribution in the DEHD plan was registered with that in the original plan, based on the isocenter. Dose distribution was not normalized, but was compared for the area receiving more than 50% of the isodose to evaluate the dose around the target using the dose difference criteria of 0.5%, 1.0%, and 2.0%, with a dose grid resolution of 0.39 mm.

III. RESULTS & DISCUSSION

A. Effects of interportal breath-hold positional error on dose distribution

Frequency histograms of generated random numbers are shown in Fig. 2. Means ± SDs of random numbers were 0.07 ± 1.12 mm (range, -3.62 to 3.59 mm), 0.12 ± 0.99 mm (range, -2.47 to 3.54 mm), and 0.12 ± 1.26 mm (range, -2.95 to 5.33 mm) in LR, SI, and AP directions, respectively. These values were comparable to those reported previously.[21]

Variations in HI, $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ for the PTV and D_{1cc} for the stomach and duodenum are summarized in Table 1. The data in the third, fourth, and fifth columns are means ± SDs of dose volume metrics from ten patients in the original treatment plan, those from 150 fractions incorporating interportal positional error, and those from averaged sums of 15 fractions for each patient, respectively. The PTV was well-covered by the planned dose, while D_{1cc} for the stomach and duodenum varied interfractionally; however, these variations were small compared

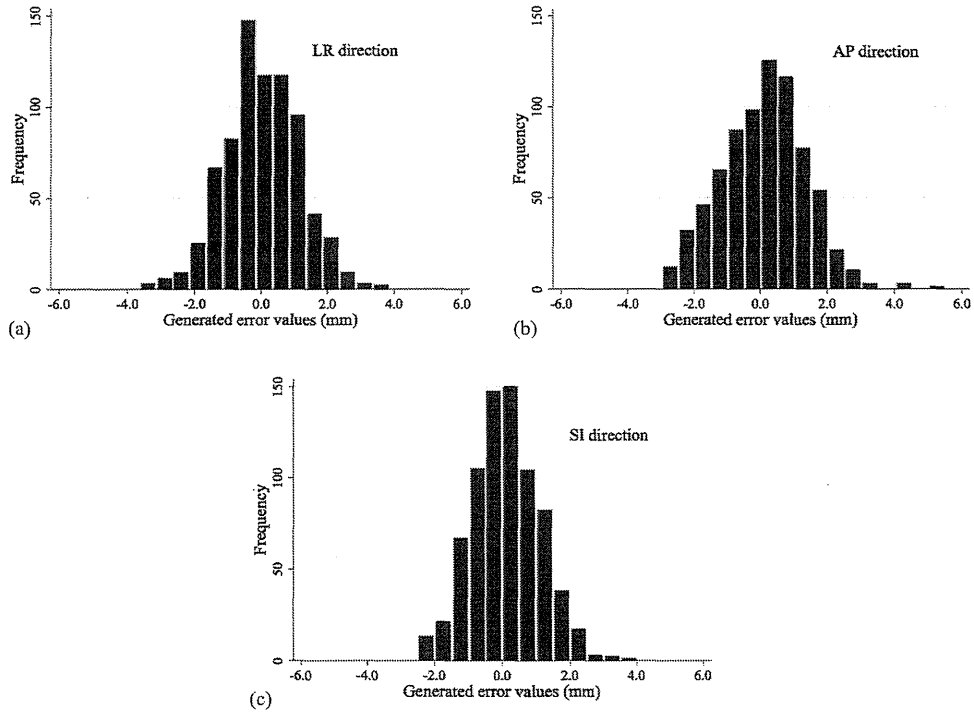

FIG. 2. Histograms of error values generated using random numbers in the (a) LR, (b) AP, and (c) SI directions.

with the original plan. Figure 3 shows the dose-volume histogram (DVH) for the case with the largest dosimetric variation in HI for PTV. The extent of the whiskers indicates the total range of variation from the original value for 15 fractions. Several investigators have indicated that the dosimetric deviations are averaged out over multiple fractions;[26,27] on this basis, the effect of interportal variation on delivered dose after 15 fractions would seem to be negligible.

TABLE 1. Variations in dose-volume metrics.

Structure	*Parameter*	*Original*	*Each Fraction*	*Total Fraction*
PTV (%)	$D_{98\%}$	93.74±6.48	93.19±6.28	93.40±6.50
	$D_{2\%}$	110.10±5.94	110.09±5.65	110.97±5.93
	$D_{50\%}$	105.80±4.72	105.67±4.55	105.62±4.74
	HI	0.164±0.041	0.170±0.042	0.167±0.041
Duodenum (cGy/fr)	$D_{1\ cc}$	233.13–255.63	219.52–262.39	231.63–252.89
Stomach (cGy/fr)	$D_{1\ cc}$	43.32–256.14	34.45–259.73	45.53–255.86

PTV = planning target volume; $D_{XX\%}$ = dose covering a volume of XX%; HI = homogeneity index; D_{1cc} = dose covering a volume of 1 cc.

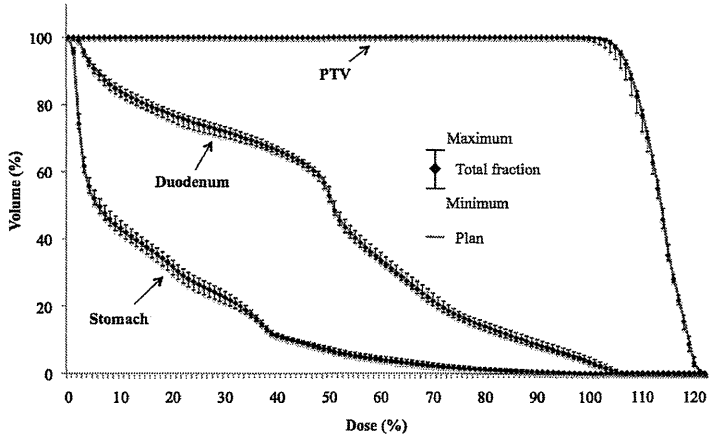

FIG. 3. DVH for the case with the largest variation in HI for PTV.

B. Evaluation of the DEHD plan

Table 2 summarizes the comparison of dosimetric parameters in HI, $D_{98\%}$, $D_{50\%}$, and $D_{2\%}$ by the mean ± SD in percentiles for the PTV and D_{1cc} by the range in cGy for the stomach and duodenum, respectively. While the BH times required in the original plan ranged from 11.3 to 16.8 sec, those in the DEHD plan were in the range 7.9–11.4 sec. Among 50 ports, BH time was longer than 10 sec in only six (12%). The reduction in BH time was in the range 23.5%–40.3%.

Means ± SDs of the pass rate of dose differences between the original and DEHD plans were 84.1% ± 14.6% (range, 33.9%–97.5%), 93.6% ± 9.9% (range, 58.1%–100.0%), and 97.9% ± 4.5% (range, 76.8%–100.0%), with criteria of 0.5%, 1.0%, and 2.0%, respectively (Table 3). The pass rate for the dose differences between the original and DEHD plans was generally high in 0.5% and 1.0%, except for patient #7. Figure 4 shows the dose difference map for the port having the worst pass rate (patient #7, port 4). Even when there were large dose differences between the original and DEHD plans, however, the dosimetric parameters in the DEHD plan were almost identical to those in the original plan (Fig. 5). The reason why large dose

TABLE 2. Comparison of dose-volume metrics between the original and DEHD plans.

Structure	*Parameter*	*Original*	*DEHD*
PTV (%)	$D_{98\%}$	93.74±6.48	93.50±6.57
	$D_{2\%}$	110.10±5.94	110.96±6.00
	$D_{50\%}$	105.80±4.72	105.58±4.77
	HI	0.164±0.041	0.165±0.042
Duodenum (cGy/fr)	$D_{1\ cc}$	233.13–255.63	233.30–254.10
Stomach (cGy/fr)	$D_{1\ cc}$	43.32–256.14	44.30–255.64

PTV = planning target volume; $D_{XX\%}$ = dose covering a volume of XX%; HI = homogeneity index; D_{1cc} = dose covering a volume of 1 cc.

TABLE 3. Pass rate of dose differences between the original and DEHD plans for each patient.

Threshold		*Pt. 1*	*Pt. 2*	*Pt. 3*	*Pt. 4*	*Pt. 5*	*Pt. 6*	*Pt. 7*	*Pt. 8*	*Pt. 9*	*Pt. 10*
0.5%	Mean (%)	83.1	95.4	86.9	88.3	86.3	87.3	52.0	80.6	90.2	91.0
	SD (%)	2.5	1.4	6.0	5.5	9.4	8.7	20.1	15.8	5.4	6.0
1.0%	Mean (%)	93.8	99.6	94.4	98.8	94.7	97.2	74.2	88.4	97.0	97.9
	SD (%)	2.9	0.4	4.0	2.2	6.5	3.2	17.1	13.3	1.8	2.6
2.0%	Mean (%)	98.4	100.0	97.3	100.0	98.1	99.9	92.7	93.7	99.4	99.9
	SD (%)	2.0	0.0	1.8	0.1	2.1	0.1	8.0	9.6	0.8	0.3

SD = standard deviation.

differences were observed may be that the MLC control points increased in the DEHD plan when recalculating the leaf motion and actual fluence map. Compared with other ports (31.1% on average), a marked increase in the MLC control points was observed for port 4 in patient #7 (39.8%), which may have caused the relatively large dose difference in actual fluence between the original and DEHD plan. In DMLC IMRT, breath-holding time was not prolonged, even when the MLC control points were increased.

The DEHD plan was capable of reducing BH time by 33%, on average, without markedly reducing the dose-volume parameters in the original plan, facilitating the treatment of patients who find prolonged BH difficult. However, this method increases the frequency of breath holding and prolongs the time the patient is required to maintain the same posture. Accordingly, it is desirable to use the DEHD plan only when difficulties in breath-hold time are expected, or large dosimetric errors in the patient's body are predicted due to poor reproducibility of the breath-holding position. Selection of the plan in consideration of these advantages and disadvantages can reduce the physical distress in patients and deviations of the actual dose distribution from that calculated in the treatment plan. When the number of ports increased from the original plan, BH time was shortened, but dose-volume metrics and dose distributions were sometimes different from the original plan. The DEHD plan uses the optimized fluence map of the original plan; thus, further optimization processes are not needed once dose-volume constraints in the original plan are satisfied, while radiation oncologists using the DEHD plan must verify dose-volume metrics and dose distributions. Additionally, medical physicists must check the machine condition and parameters in the radiation treatment planning system and perform additional DQA if there are large differences between the calculated and measured doses. An additional advantage of our proposed method is that interportal BH positional errors can be better averaged out. The dose distribution in the DEHD plan can thus be closer to the planned dose distribution than with the original plan.

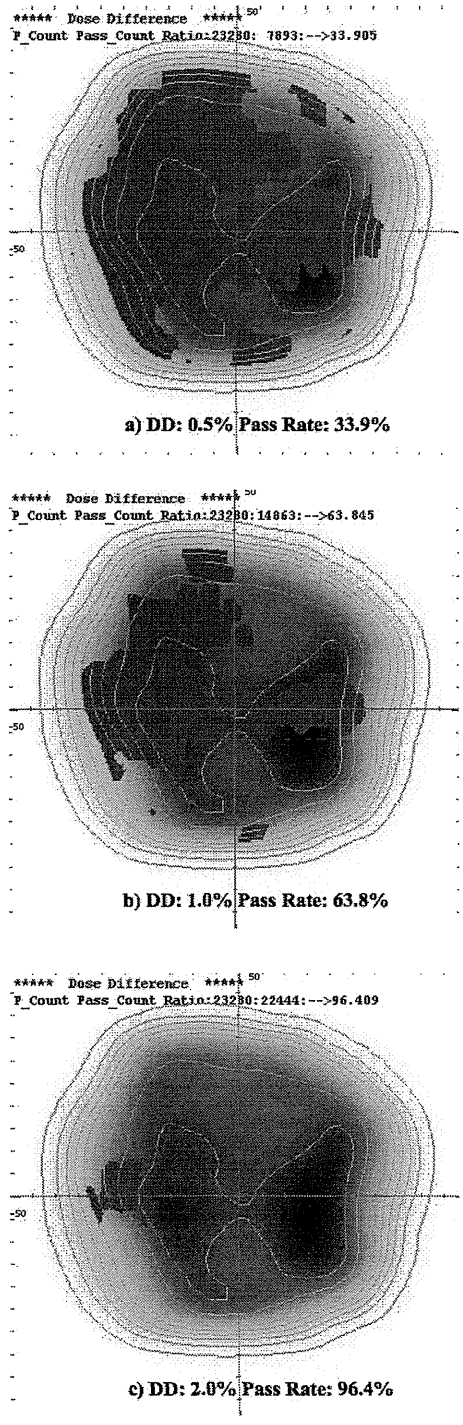

FIG. 4. Comparison of dose-difference maps between the original and DEHD plans for the case with the worst pass rate. The red areas indicate failure, with criteria of (a) 0.5%, (b) 1.0%, and (c) 2.0% for the area receiving more than 50% of the dose. The isodose lines displayed in the interval 10% are from the 10% to the 90% isodose lines.

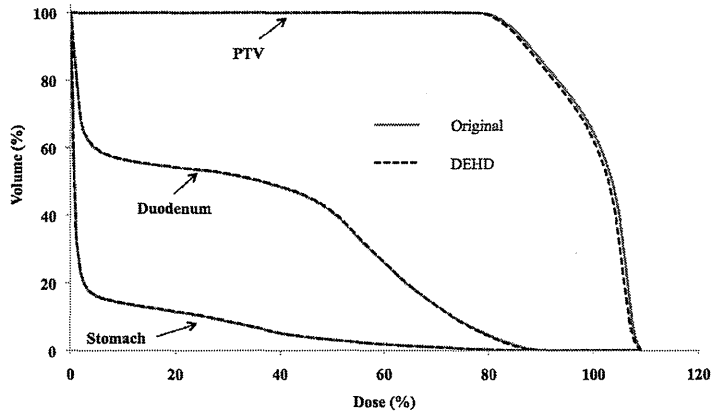

FIG. 5. DVH of the original and DEHD plans for patient #7.

IV. CONCLUSIONS

We demonstrated that the effects of interportal error on dose distribution in BH-IMRT are negligible. Additionally, we propose a new method of treatment planning, called the "DEHD plan". The DEHD plan can shorten BH time without substantially reducing dose-volume metrics and without increasing DQA workload, compared with that required for a multiport plan, because only one of the two identical beams is measured. Finally, the effects of interportal error on dose distribution can be reduced through using the DEHD plan.

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Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy

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What's known on the subject? and What does the study add?

- It is known that a prostate cancer gene 3 (PCA3) urine assay is superior to serum PSA level or PSA-related indices for predicting a positive biopsy result in European and US men.
- This is the first report on PCA3 in a large cohort of Japanese men. The diagnostic value of the PCA3 score in Japanese men was similar to those reported in European and US men. The study concludes that a combination of PSA density and PCA3 score may be useful for selecting patients who could avoid an unnecessary biopsy.

Objective

- To examine the diagnostic performance of the prostate cancer gene 3 (PCA3) score for prostate cancer in Japanese men undergoing prostate biopsy.

Patients and Methods

- This Japanese, multicentre study included 647 Asian men who underwent extended prostate biopsy with elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE).
- Urine samples were collected after DRE.
- The PCA3 score was determined using a PROGENSA PCA3 assay and correlated with biopsy outcome. Its diagnostic accuracy was compared with that of serum PSA level, prostate volume (PV), PSA density (PSAD), and free/total PSA ratio (f/t PSA).

Results

- A total of 633 urine samples were successfully analysed (the informative rate was 98%). Median PSA was 7.6 ng/mL.
- Biopsy revealed cancer in 264 men (41.7%). The PCA3 score for men with prostate cancer was significantly higher than that for men with negative biopsies (median PCA3 score: 49 vs. 18; $P < 0.001$). The rate of positive biopsy was 16.0% in men with a PCA3 score of <20 and 60.6% in those with a PCA3 score of ≥50.
- Using a PCA3 score threshold of 35, sensitivity and specificity were 66.5 and 71.6%, respectively.
- The area under the curve of the PCA3 score was significantly higher than that of the f/t PSA in men with PSA 4–10 ng/mL (0.742 vs 0.647; $P < 0.05$).
- In men with PSAD < 0.15 and PCA3 < 20, only three (4.2%) out of 72 men had prostate cancer.

Conclusions

- The PCA3 score was significantly superior to f/t PSA in predicting a positive biopsy result for prostate cancer in Japanese men with PSA 4–10 ng/mL.
- The combination of PSAD and PCA3 score may be useful for selecting patients who could avoid an unnecessary biopsy.

Keywords

Japanese men, PCA3 urine assay, prostate cancer

Introduction

Serum PSA level has been widely used to detect prostate cancer [1]. It is organ-specific, but not cancer-specific. Several conditions, including BPH and prostatitis, may be associated with an elevated PSA level. An elevated PSA level is likely to be associated with prostate cancer, but the low specificity of PSA limits its use as a screening test and

results in a large number of unnecessary biopsies [2]. Several modifications of PSA-related indices such as PSA isoforms and volume-referenced PSA have been investigated to improve the specificity of PSA in detecting prostate cancer [3–5]. Free/total PSA ratio (f/t PSA) is widely used in clinical practice to differentiate prostate cancer from BPH in men with grey zone PSA levels, but this does not have sufficient specificity to reduce unnecessary biopsies. Thus, more accurate and reliable assessments are needed to select candidates for prostate biopsy.

Bussemakers et al. [6]reported that prostate cancer gene 3 (PCA3) produces an untranslated, prostate-specific messenger RNA (mRNA) that is highly overexpressed in prostate cancer tissue compared with its level in normal or benign tissue. Several studies have shown that PCA3 urine assay is superior to serum PSA level or various PSA isoforms for predicting prostate cancer in European and US men, and it could be used as a diagnostic tool to select biopsy candidates [7–10]. We have previously demonstrated the high specificity of PCA3 urine assay in detecting prostate cancer in a limited number of Japanese men at a single institution [11]. In the present multicentre study, we investigated the diagnostic performance of this assay in a large cohort of Japanese men.

Methods

The study protocol was approved by the institutional review boards and all men provided written informed consent before enrolment in the present study. A total of 647 men with elevated serum PSA levels and/or an abnormal DRE were enrolled. They underwent systematic extended prostate biopsy (≥8 cores) at one of four Japanese institutions (Kyoto Prefectural University of Medicine, Japanese Red Cross Medical Centre, University of Tsukuba and Kinki University) from 2009 to May 2011. The ethnic origin of all patients was Asian. Among the 647 cases, 158 had a previous negative biopsy. The exclusion criteria were as follows: previous history of prostate cancer, taking medication known to affect serum PSA levels, UTIs, and history of invasive treatment for BPH. The first voided urine sample was collected after a DRE, and the urine specimen was examined using a PROGENSA PCA3 assay according to a previously described method [11]. The PCA3 score was determined using PCA3 mRNA copy divided by PSA mRNA copy. The f/t PSA was measured in men with PSA 4–10 ng/mL. Prostate volume (PV) was measured using ultrasonography and PSA density (PSAD) was calculated by dividing PSA by PV. Clinical and pathological outcomes such as clinical stage, Gleason score and percentage of positive cores (% positive cores) in men diagnosed with prostate cancer were correlated with PCA3 score. The % positive cores was calculated as the number of positive cores divided by the number of cores taken, and patients were divided into two groups according to % positive cores (≤33% or >33%). Indolent cancer was defined, according to the Epstein criteria, as clinical stage T1c, PSAD < 0.15, Gleason score ≤ 6, and <3 positive cores on a six-core biopsy, which was replaced by % positive cores ≤ 33 with biopsy sampling of more than six cores [12]. The Mann–Whitney test was used to compare continuous variables among the groups. The chi-squared test was used to assess nominal variables. Bivariate analysis (Pearson's correlation coefficient '*r*') was used to test the linearity of relationships among the variables. Areas under the receiver–operator curves (AUCs) were compared. Multiple stepwise logistic regression analysis was used to determine the significant predictors of positive biopsy among variables such as repeated biopsy or not, PSA, PV, PSAD and PCA3 score. These statistical analyses were performed using commercially available software (SPSS version 12.0, Chicago, IL, USA). A P value of <0.05 was considered to indicate statistical significance.

Results

Among 647 urine samples, 633 were successfully analysed (the informative rate was 98%). The median (range) age, PSA level and number of biopsy cores taken were 69 (42–89) years, 7.6 (1.4–1908) ng/mL and 12 (6–59), respectively. Two patients had a six-core biopsy. There was no relationship between the PCA3 score and serum PSA level ($r = 0.049$, nonsignificant). Prostate biopsy was positive for prostate cancer in 264 men (41.7%). The characteristics of the men with positive and negative biopsies are shown in Table 1. The median PCA3 score in men with prostate cancer was significantly higher than that in those without prostate cancer (49 vs 18, $P < 0.001$). The positive rate of biopsy is shown in Table 2. We excluded all men who had a PSA level > 50 ng/mL and men who had initial biopsy with PSA of 20–50 ng/mL from further analyses because of the high yield of positive biopsy results; thus, the remaining 578 men were entered for analysis. The percentage of men with positive biopsy increased with increasing PCA3 score (Fig. 1). In men with a PCA3 score < 20, 16.0% (38/237) had a positive biopsy. When the PCA3 score was ≥50, the percentage of patients with a positive biopsy was 60.6% (106/175). Sensitivity, specificity, positive and negative predictive values of PCA3 scores at different PSA thresholds are shown in Table 3. Using a PCA3 threshold of 35, the sensitivity, specificity and diagnostic accuracy were 66.5, 71.6 and 69.7%, respectively. The AUCs of PSA, PV, PSAD and PCA3 score in 561 available men were 0.583, 0.706, 0.712 and 0.748, respectively. There was a significant difference in AUC between PSA and PCA3 score ($P < 0.001$), but not between PSAD and PCA3 score. Thirty-eight out of 408 men with PSA of 4–10 ng/mL had missing values of either PV or f/t PSA. In 370 available men

Table 1 Characteristics of patients with negative and positive biopsy results.

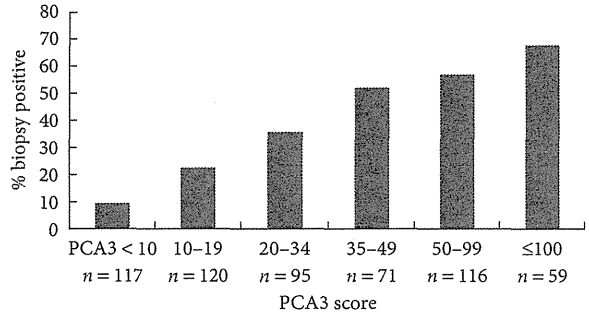
Characteristic	Negative biopsy, $n = 369$	Positive biopsy, $n = 264$	P
	Median (range)	Median (range)	
Age, years	67 (42–89)	71 (49–88)	<0.001
PSA, ng/mL	7.0 (1.4–42.6)	9.0 (2.2–1908)	<0.001
PV*, mL	38 (9.4–130)	29.1 (8.2–109)	<0.001
PSAD	0.18 (0.03–1.38)	0.36 (0.07–80.84)	<0.001
No. of cores	12 (6–59)	12 (6–40)	N.S.
PCA3 score	18 (0–381)	49 (1–288)	<0.001

**22 cases not available. N.S., nonsignificant.*

Table 2 Positive rate of prostate cancer by serum PSA range.

PSA ng/mL	Total		Initial biopsy		Repeat biopsy	
	n	Prostate cancer (%)	n	Prostate cancer (%)	n	Prostate cancer (%)
≤4	22	5 (22.7)	21	5 (23.8)	1	0 (0)
4–10	408	140 (34.3)	316	120 (38.0)	92	20 (21.7)
10–20	131	64 (48.8)	85	44 (51.8)	46	20 (43.5)
20–50	46	29 (63.0)	29	23 (79.3)	17	6 (37.9)
>50	26	26 (100)	25	25 (100)	1	1 (100)
Total	633	264 (41.7)	476	217 (45.6)	157	47 (29.9)

Fig. 1 Percentage of men with positive biopsy by PCA3 score range ($N = 578$).



with PSA of 4–10 ng/mL, the AUCs of PSA, f/t PSA, PV, PSAD and PCA3 score were 0.557, 0.647, 0.686, 0.692 and 0.742, respectively. There was a significant difference in AUC between f/t PSA and PCA3 score ($P < 0.05$), but not between PSAD and PCA3 score (Fig. 2). On univariate regression analysis, all variables had a significant association with biopsy outcome. Multivariate logistic regression analysis showed that PCA3 score ($P < 0.001$), PSAD ($P < 0.001$), PV ($P < 0.01$) and repeated biopsy ($P < 0.01$) were independent factors predicting biopsy outcome (Table 4). Totals of 21.1% (32/152), 22.9% (27/118) and 51.5% (150/291) of patients had a positive biopsy in patients with PSAD < 0.15, 0.15–0.2 and ≥0.2, respectively. The percentage of men with positive biopsy according to the combination of PSAD and PCA3 score is shown in Fig. 3. The percentage of patients with a positive biopsy increased with higher PCA3 scores in subgroups based on PSAD. Only three (4.1%) out of 72 cases with PSAD < 0.15 and PCA3 score < 20 had prostate cancer. A total of 43% had a positive biopsy in men with PSAD < 0.15 and PCA3 score ≥50. In 264 men diagnosed with prostate cancer, a total of 72, 103 and 89 cases had Gleason scores ≤ 6, 7, and ≥8, respectively. Median (range) PCA3 scores in men with Gleason scores ≤ 6, 7 and ≥8 were 45 (4–280), 51 (4–288), and 45 (1–250), respectively. There was no significant difference in PCA3 score among these three groups. A total of 88, 133, 35 and eight patients had clinical stage T1c, T2, T3, and T4, respectively. Median (range) PCA3 scores in men with clinical stage T1c, T2, T3, and T4 were 44 (6–242), 55 (4–280), 49 (1–288), and 51 (15–123), respectively. There was no significant difference in PCA3 score among the four categorical groups of clinical stage. There was a significant association between PCA3 score and % positive cores ($r = 0.166$, $P < 0.01$). Data on % positive cores was not available in two patients. A total of 164 and 98 cases had % positive cores ≤ 33, and >33, respectively. A total of 12 and 248 cases had indolent cancer and significant cancer, respectively. There was no significant difference in PCA3 score between % positive cores ≤ 33 and >33 (median PCA3 score 47 vs 58), or between indolent cancer and significant cancer (median PCA3 score 39 vs 49).

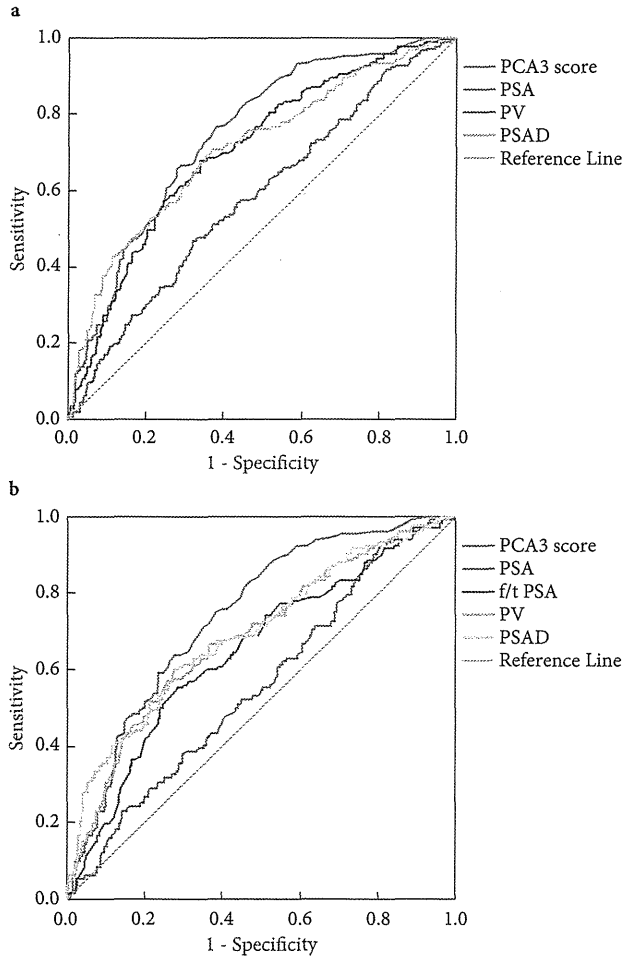
Discussion

In the present study, we investigated the ability of a PCA3 urine assay to predict the prostate biopsy outcome in a

Table 3 Sensitivity, specificity, positive and negative predictive values at different PCA3 score thresholds.

PCA3 score	Sensitivity	Specificity	Positive predictive value	Negative predictive value
10	94.9	29.2	44.3	90.6
20	82.3	54.8	51.9	84.0
35	66.5	71.6	58.1	78.3
50	49.3	81.0	60.6	73.0
100	18.6	94.8	67.8	66.3

Fig. 2 A, Receiver - operator curve (ROC) analysis to predict positive biopsy results (n = 561), PSA: 0.583, PV: 0.706, PSAD: 0.712, PCA3 score: 0.748. PSA vs. PCA3 score: $P < 0.001$, PV, PSAD vs. PCA3 score N.S. **B**, ROC analysis to predict positive biopsy result in patients with PSA between 4 and 10 ng/mL (n = 370), PSA: 0.557, f/t PSA: 0.647, PV: 0.686, PSAD: 0.692, PCA3 score: 0.742, PSA vs PCA3 score $P < 0.001$, f/t PSA vs. PCA3 score: $P < 0.05$, PV, PSAD vs. PCA3 score N.S.



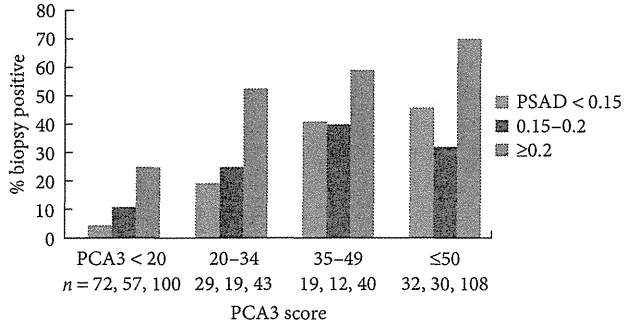
large cohort of patients from four major institutions in Japan. We found the highly informative specimen rate of 98% using a PROGENSA PCA3 assay, which verified the results of multiple studies [7–11]. We observed an increasing incidence of prostate cancer in men with a higher PCA3 score. The diagnostic performance of PCA3 urine assay for prostate cancer was excellent, with an AUC of 0.748 in Japan, compared with other reports in North America and Europe ranging from 0.66 to 0.69 [8–10,13]. Adam et al. [14] reported that the AUC of PCA3 was 0.7054 in a South African setting consisting of 68% black men. At a PCA3 threshold of 35, which is considered to be a better balanced value between sensitivity and specificity, the specificity of the PCA3 score was 71.6% in Japanese men, compared with 72–76% in North American and European men and 50% in South African men. These results showed that the diagnostic performance of PCA3 assay in Japan was similar to that reported in different regions and ethnic groups.

Free/total PSA ratio is widely used to stratify the risk of prostate cancer in men with PSA 4–10 ng/mL, and a lower f/t PSA is more likely to be found in association with prostate cancer [4]. In the present study, we found that the diagnostic performance of PCA3 score surpassed that of f/t PSA in men with PSA 4–10 ng/mL. The AUC of the PCA3 score was highest among the variables analysed and it was significantly higher than that of f/t PSA (0.742 vs 0.647; $P < 0.05$). In the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, 1140 men who had a negative baseline biopsy received a PCA3 score before repeat biopsy at 2 years [15]. In its largest repeat biopsy study to date, the AUCs of PCA3 score, PSA, and f/t PSA were 0.693, 0.612 and 0.637, respectively. A significant difference was found between PCA3 score and PSA, but the difference between PCA3 score and f/t PSA did not reach statistical significance ($P = 0.065$). In 463 European men with repeat biopsy, the AUC of PCA3 score was higher than that of f/t PSA (0.658 vs 0.578); however, the difference in AUCs between PCA3 score and f/t PSA did not reach statistical significance either [10]. We confirmed that PCA3 score was significantly superior to f/t PSA and PSA in predicting biopsy outcome in Japanese men with grey zone PSA levels.

Table 4 Univariable and multivariable logistic regression analysis for positive biopsy.

Variable	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Repeat biopsy	0.626	0.422–0.930	<0.05	0.521	0.319–0.849	<0.01
PSA	1.058	1.022–1.096	<0.01			N.S.
PV	0.955	0.942–0.968	<0.001	0.978	0.963–0.992	<0.01
PSAD	60.885	18.671–198.536	<0.001	18.883	4.805–74.208	<0.001.
PCA3 score	1.017	1.013–1.022	<0.001	1.015	1.010–1.020	<0.001

Fig. 3 Percentage of men with positive biopsy by combination of PCA3 score range and PSAD range.



Multivariable logistic regression showed that PCA3 score ($P < 0.001$), PSAD ($P < 0.001$), PV ($P < 0.01$) and repeated biopsy ($P < 0.01$) were independent predictors of positive biopsy in the present study. Several studies showed that PCA3 score was significantly cooperating with PSA and PV for predicting prostate cancer [9,10,13]. PSA correlates with PV in men without prostate cancer; thus, PSAD (PSA divided by PV) was used for more accurate assessment to improve the specificity in diagnosis of prostate cancer; however, the commonly used PSAD threshold of 0.15 could not detect > 40% of cancers, resulting in limited usefulness in a routine clinical setting [5]. In the present study, 21.1% of men with PSAD < 0.15 had a positive biopsy. Thus, when a PSAD threshold value of 0.15 was applied in our population, a considerable number of prostate cancer cases were missed. When the PCA3 score was combined with PSAD, we observed that the rate of positive biopsy increased, even in the subgroup of men with PSAD < 0.15 (Fig. 3). When the PCA3 score was <20 in men with PSAD < 0.15, only three (4.1%) out of 72 men had prostate cancer. By contrast, 43% of men with PCA3 score ≥50 and PSAD < 0.15 had a positive biopsy. The combination of PSAD and PCA3 score stratifies the risk of prostate cancer and predicts a low risk of prostate cancer, suggesting that these men could avoid unnecessary biopsy. It is notable that these three patients with cancer (PSAD < 0.15 and PCA3 score <20) had significant cancer with % positive cores of ≤33 and Gleason score > 6 as biopsy pathological features.

Several studies have shown the significant relationship between PCA3 score and tumour volume in prostatectomy specimens and the ability of PCA3 score to discriminate low-volume/low-grade cancer with the aim of selecting patients who are candidates for active surveillance [16,17]. Ploussard et al. [17]reported that a high PCA3 score of >25 was an important predictor of large tumour volume with an odds ratio of 5.4 ($P = 0.1$) and significant cancer with an odds ratio of 12.7 ($P = 0.003$). In the present study, we found a significant relationship between PCA3 score and % positive cores; however, there was no difference in PCA3 score between % positive ≤ 33 and >33, or among subgroups by Gleason score and clinical stage. Further investigation of the correlation between PCA3 score and pathological outcomes on prostatectomy specimens will be needed in Japan.

In the present cohort, men with a wide range of PSA levels were enrolled. A PCA3 urine assay would be irrelevant in men with a high PSA level (the positive rate of prostate cancer was 100% in men with PSA > 50 ng/mL, and 79.3% in men with PSA 20–50 ng/mL at initial biopsy); thus, these were excluded from the analysis for prediction of biopsy outcome. Furthermore, not all men received prostate volume measurement because this was a multi-institutional study. These features might have influenced the results.

In conclusion, this Japanese multicentre study shows that the PCA3 urine assay could improve the prediction of prostate cancer and may help in selecting men who might benefit from prostate biopsy. The percentage of patients with positive biopsy increased with higher PCA3 scores. PCA3 score was superior to f/t PSA for predicting prostate cancer in patients with PSA 4–10 ng/mL. A combination of PSAD and PCA3 score may be useful for selecting patients who could avoid an unnecessary biopsy.

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Conflict of Interest

None declared.

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Abbreviations: PCA3, prostate cancer gene 3; f/t PSA, free/total PSA ratio; mRNA, messenger RNA; PV, prostate volume; PSAD, PSA density; AUC, area under the receiver–operator curve.

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Vaginal tolerance of CT based image-guided high-dose rate interstitial brachytherapy for gynecological malignancies

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Abstract

Background: Purpose of this study was to identify predictors of vaginal ulcer after CT based three-dimensional image-guided high-dose-rate interstitial brachytherapy (HDR-ISBT) for gynecologic malignancies.

Methods: Records were reviewed for 44 female (14 with primary disease and 30 with recurrence) with gynecological malignancies treated with HDR-ISBT with or without external beam radiation therapy. The HDR-ISBT applicator insertion was performed with image guidance by trans-rectal ultrasound and CT.

Results: The median clinical target volume was 35.5 ml (2.4-142.1 ml) and the median delivered dose in equivalent dose in 2 Gy fractions (EQD_2) for target volume D_{90} was 67.7 Gy (48.8-94.2 Gy, doses of external-beam radiation therapy and brachytherapy were combined). For re-irradiation patients, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 91.1 Gy, 100.9 Gy, 260.3 Gy, 212.3 Gy, 170.1 Gy, 117.1 Gy, 105.2 Gy, and 94.7 Gy, respectively. For those without prior radiation therapy, median EQD_2 of D_{2cc} for rectum and bladder, $D_{0.5cc}$, D_{1cc}, D_{2cc}, D_{4cc}, D_{6cc} and D_{8cc} for vaginal wall was 56.3 Gy, 54.3 Gy, 147.4 Gy, 126.2 Gy, 108.0 Gy, 103.5 Gy, 94.7 Gy, and 80.7 Gy, respectively. Among five patients with vaginal ulcer, three had prior pelvic radiation therapy in their initial treatment and three consequently suffered from fistula formation. On univariate analysis, re-irradiation and vaginal wall D_{2cc} in EQD_2 was the clinical predictors of vaginal ulcer ($p = 0.035$ and $p = 0.025$, respectively). The ROC analysis revealed that vaginal wall D_{2cc} is the best predictor of vaginal ulcer. The 2-year incidence rates of vaginal ulcer in the patients with vaginal wall D_{2cc} in EQD_2 equal to or less than 145 Gy and over 145 Gy were 3.7% and 23.5%, respectively, with a statistically significant difference ($p = 0.026$).

Conclusions: Re-irradiation and vaginal D_{2cc} is a significant predictor of vaginal ulcer after HDR-ISBT for gynecologic malignancies. Three-dimensional image-guided treatment planning should be performed to ensure adequate target coverage while minimizing vaginal D_{2cc} in order to avoid vagina ulcer.

Keywords: Gynecologic brachytherapy, High-dose-rate brachytherapy, Interstitial brachytherapy, Vaginal ulcer

Introduction

High-dose rate intracavitary brachytherapy (HDR-ICBT) is an established method in the management of gynecological malignancies, especially in cervical cancer. However, in patients with a narrow vagina, short uterine cavity, distal vaginal extension, and bulky tumors in which the optimal dose distribution cannot be obtained by intracavitary brachytherapy (ICBT), interstitial brachytherapy (ISBT) is employed. Also in patients with bulky postoperative central pelvic recurrence, ISBT has proven to be effective [1-5]. With the advent of image-guided brachytherapy it has become possible to assess the dose volume histogram (DVH) in brachytherapy. Several studies have validated the D_{2cc} as a predictor of rectal and bladder toxicities for ICBT [6] or for ISBT [7]. D_{2cc} of the rectum and bladder have been introduced into daily clinical practice of gynecological image-guided brachytherapy. However in ICRU 38 vagina was not recognized as organ at risk

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