Table 5. Comparison of positive predictive values (PPV) by core and by patient, number of patients who saved biopsies, and number of missing cancers when using directed biopsies by transrectal ultrasonography (TRUS), power Doppler ultrasonography (PDUS), transrectal real-time tissue elastography (TRTE) and combination of PDUS and TRTE, with when using only systematic biopsies in patients with PSA levels >10 ng/ml (n = 45)

Test	PPV n/N cores (%)	PPV n/N Pts. (%)	Biopsies saved n/N Pts. (%)	Missing cancers n/N Pts. (%)
TRUS-directed	24/40 (60)	11/16 (69)	29/45 (64)	10/21 (48)
PDUS-directed	33/55 (60)	17/24 (71)	21/45 (47)	4/21 (19)
TRTE-directed	30/49 (61)	16/22 (73)	23/45 (51)	5/21 (24)
PDUS+TRTE-directed*	33/59 (56)	18/25 (72)	20/45 (44)	3/21 (14)
Systematic only	51/360 (14)	19/45 (42)	None	2/21 (10)

* PDUS+TRTE-directed biopsy indicates that taking biopsy cores from the suspicious areas in either PDUS or TRTE image as well as the overlapping suspicious areas in both PDUS and TRTE images.

though there was not statistically significant difference in these combinations. The combination of all three ultrasound techniques did not add any diagnostic values compared with the combination of PDUS and TRTE.

ROC curve analysis demonstrated that TRTE had highest area under ROC curve without statistical significance compared with PDUS and TRUS (Fig. 2).

Tables 3, 4 and 5 compare positive predictive value by core and by patient, number of patients who saved biopsies and number of missing cancers when using directed biopsies by TRUS, PDUS, TRTE and combination of PDUS and TRTE, when using only systematic biopsies in overall patients as well as in patients with PSA levels of 4 to 10 ng/mL and >10 ng/mL, respectively. In overall patients, the detection rate of directed biopsy from suspicious area by either TRTE or PDUS (TRTE+PDUS-directed biopsy) was 29% (31/107) by patient and was comparable with systematic biopsy (31%, 33/107, p = 0.86), whereas the detection rate of TRTE+PDUS-directed biopsy by core (55/111, 50%) was significantly higher than systematic biopsy (132/856, 15%, $p < 0.0001$). In patients with PSA levels from 4 to 10 ng/mL, there were 28% (5/18) of cancer patients who would have been undetected when using either PDUS + TRTE-directed biopsies or systematic octant biopsies. In patients with PSA levels >10 ng/mL, there were 14% (3/21) and 10% (2/21) of patients missing when using PDUS + TRTE-directed biopsies and systematic octant biopsies, respectively.

Because both DRE and TRTE measures hardness of prostatic tissue, we sought to evaluate the relationship between DRE and TRTE (Table 6). As a result, TRTE was significantly correlated with DRE with moderate agreement ($p < 0.0001$, κ = 0.469). Most of the patient with positive DRE-demonstrated positive TRTE (23/28, 82%), whereas fewer patients with negative DRE demonstrated negative TRTE (58/79, 73%).

Table 6. Relationship between digital rectal examination (DRE) and transrectal real-time elastography (TRTE)

	DRE-positive	DRE-negative
TRTE-positive	23	21
TRTE-negative	5	58

κ = 0.469 ($p < 0.0001$, 95%CI = 0.290-0.648).

Interobserver agreement for the independent assessment of ultrasound findings are reported in Table 7. The kappa values for both PDUS and TRTE demonstrated moderate agreement between examiner and readers (0.439 and 0.578 *vs.* readers 1 and 2, respectively), whereas there was fair (0.317 *vs.* reader 1) or minor (0.079 *vs.* reader 2) agreement in TRUS.

Uni- and multivariate regression analysis to predict high (≥8) Gleason score is shown in Table 8. On multivariate analysis, TRTE was the only significantly independent predictor for diagnosing high grade-prostate cancer (p = 0.0365, OR = 10.449, 95% CIs 1.1415-266.00).

Table 9 shows the cancer detection rate by Gleason score. TRTE detected 100% (13/13) of prostate cancer with high Gleason score, whereas PDUS and TRUS did not detect 1 (8%) and 4 (31%) cancers, respectively.

DISCUSSION

The phenomenon of elastography or strain imaging was first described by Ophir et al. (1991). Since its

Table 7. Interobserver agreement between the examining physician and a blinded reader as expressed by κ coefficients for the evaluation of transrectal ultrasonography (TRUS), power Doppler ultrasonography (PDUS) and transrectal real-time tissue elastography (TRTE)

	Kappa: examining physician *vs.* reader no. 1	Kappa: examining physician *vs.* reader no. 2
TRUS	0.317	0.079
PDUS	0.439	0.578
TRTE	0.472	0.537

Table 8. Uni- and multivariate regression analysis to predict high (≥8) Gleason score by using variables of age, serum PSA level, prostate volume, transrectal ultrasonography (TRUS), power Doppler ultrasonography (PDUS) and transrectal real-time tissue elastography (TRTE)

Variables	Univariate *p*-value	Multivariate *p*-value	Odds ratio	Lower 95% CI	Upper 95% CI
Age	0.2113	0.4062	4.9140	0.1180	270.27
Serum PSA level	0.0040	0.3210	5.1894	0.0009	5.0891
Prostate volume	0.0576	0.8160	0.5235	0.0115	1136.6
DRE	0.0803	0.2677	2.4500	0.5069	13.661
TRUS	0.0006	0.3930	1.9524	0.4314	10.739
PDUS	0.0013	0.4088	2.9915	0.2346	78.168
TRTE	<0.0001	0.0365	10.449	1.1415	266.00

invention, this concept has been proposed for elasticity imaging of a wide range of tissues, including the breast (Garra et al. 1997), thyroid (Lyshchik et al. 2005) and prostate (Cochlin et al. 2002). Elastography has been used clinically to examine a variety of breast lesions in patients, and it has been concluded that this modality may be useful for differentiating malignant from benign masses (Garra et al. 1997). In a pilot study reported by Frauscher et al. (2005), patients with clinically localized prostate cancer who underwent radical prostatectomy were examined prospectively. TRTE detected 28 of the 32 cancer foci (sensitivity 88%). The by-patient analysis demonstrated that TRTE detected at least one cancer foci in each of the 15 patients. Therefore, they concluded that TRTE of the prostate is a sensitive new imaging modality for the detection of prostate cancer. Miyanaga et al. (2006) described a preliminary report for the utility of TRTE in 29 patients with biopsy-proven prostate cancer. TRTE successfully detected 93% (27 patients) of the cancerous lesions. Lacking the comparison with normal glands or hypertrophic glands, they commented that the establishment of diagnostic criteria is necessary.

To our knowledge, this is the first study that evaluates the grading system of TRTE in the diagnosis of prostate cancer. In this study, we used the same grading system proposed for the diagnosis of breast cancer (Itoh et al. 2006). The same scoring system was applied successfully applied for the diagnosis of thyroid cancer (Rago et al. 2007). In contrast with the optimal threshold score of 4 (probably carcinoma; strain at the periphery of the hypoechoic lesion, with sparing of the center of the lesion) to diagnose breast and thyroid cancers, our study showed the best cutoff score was 3 (indeterminate; focal asymmetric lesion without strain not related to hypoechoic lesion) to diagnose prostate cancer. To diagnose breast and thyroid cancers, main focus should be paid to distinguish malignant tissue from fibrosis in breast cancer and adenoma in thyroid cancer, which appear to be hypoechoic nodules in gray scale ultrasound (Itoh et al. 2006; Rago et al. 2007). To diagnose prostate cancer, however, we have to distinguish malignant from benign tissue in the echogenic or isoechoic lesions because recent cases are more likely to be echogenic or isoechoic by TRUS, as previously mentioned. Thus, it is apparently important to look at the tissue elasticity in the normal (isoechoic) prostatic lesions.

As reported by König et al. (2005), real-time elastography should not be interpreted without considering the conventional B-mode image at the same time because stiffer tissue, *e.g.*, prostatolithiasis, chronic prostatitis or benign nodes of prostate hyperplasia can lead to pathologic elastograms (Figs. 3, 4). The examiner can easily recognize prostatolithiasis on B-mode image; however, the discrimination of cancer focus from hyperplastic nodules or chronic prostatitis is still challenging. Currently no other ultrasound techniques can clearly discriminate cancer focus from these benign conditions. A possible direction for TRTE to solve this problem is to develop a diagnostic analyzer for given TRTE images.

In this study, all identified tumors in the prostate demonstrate stiffer characteristics than surrounding normal tissue by TRTE. However, there are potentially more compliant variants of prostate cancers, *i.e.*, mucinous, adenoid cystic/basal cell, carcinoid, transitional cell or squamous cell carcinomas. They can occur in a pure form or in association with conventional adenocarcinomas; although these variants represent only minor part of the entire cancers (<10%) (Begnami et al. 2007). The evaluation of TRTE image on these variants is yet to be

Table 9. Tumor detection rate by Gleason score for transrectal ultrasonography (TRUS), power Doppler ultrasonography (PDUS) and transrectal real-time tissue elastography (TRTE)

		No. detected (% sensitivity)		
Gleason score	No. Pts	TRUS	PDUS	TRTE
6	10	3 (30)	6 (60)	5 (50)
7	17	9 (53)	15 (88)	12 (71)
8	9	5 (56)	8 (89)	9 (100)
9	4	4 (100)	4 (100)	4 (100)

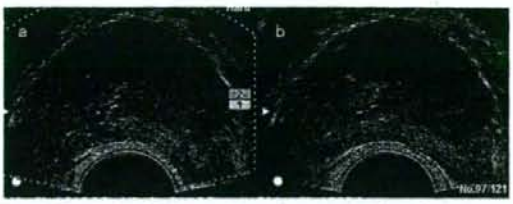

Fig. 3. Example of false positive elastography finding in patient with benign prostatic hyperplasia. There was a slightly hypoechoic lesion with small calcification in the right transition zone at the B-mode image (b). The elastography image (a) showed the center of the hypoechoic lesion in blue (no strain) and the periphery of the lesion in green (minimal strain) scoring 4 by elastography score system. Biopsy core from the right transition zone was histologically confirmed with benign prostatic hyperplasia. The blue area was also visible in the left peripheral zone with a mosaic patternlike appearance. This alteration was not reproducible after tilting the ultrasound probe.

done by accumulating the number of patients with prostate cancer.

We observed that prostate cancer can be detected with high sensitivity using TRTE, in addition to conventional diagnostic modalities. The result of our ROC curve analysis suggests that TRTE may have a diagnostic performance that is better than, or at least equal to, that of conventional US including PDUS. Systematic-only biopsy scheme would have been missing 28% and 10% of cancers in patients with the PSA levels of 4–10 ng/mL and >10 ng/mL, respectively. Image-directed biopsy improved sensitivity of 7/40 (18%) in overall patients over systematic 8-core biopsy protocol. To maximize cancer detection, we recommend a targeted biopsy strategy from the suspicious area by PDUS and TRTE, in addition to systematic biopsy strategy.

Moreover, TRTE identified all high-grade carcinoma regardless of the location of the tumor or prostate size. From a diagnostic point of view, our findings suggest that TRTE is useful for characterizing prostatic lesions in general and has the potential to allow differentiation between malignant and benign lesions. To answer the question of whether TRTE will be able to increase the detection rate of prostate cancer we need prospective, randomized study to compare the cancer detection rate between patients undergoing conventional transrectal ultrasound and TRTE.

Because the basic idea of TRTE is to measure the stiffness or hardness in the prostate, the use of TRTE is assumed to be the only supplement to DRE. Although this study showed a moderate correlation between TRTE and DRE, a considerable number of patients with false-negative DRE may produce underestimates of disease without using TRTE.

We must note the discrepancy of diagnostic power (sensitivity and specificity) by means of PDUS in the current and previous study (70% *vs.* 98% and 75% *vs.* 99% in sensitivity and specificity, respectively) (Okihara et al. 2000). This may be related to the recent series of patients having larger average volume of prostate (50.4 *vs.* 40.1, $p < 0.0001$) and proportionally smaller tumors with the stage migration. In fact, among nine patients diagnosed with prostate cancer and missed by both PDUS and TRTE in this study, five patients had only one positive core with <1 mm involvement of cancer and a Gleason score of 6.

The main limitation of TRTE is that the extent of tissue compression influences the elasticity image and, therefore, may compromise the diagnostic quality, especially when used by a novice. It takes some practice to be able to exert appropriate pressure on the surface of the prostate. Examiners must attempt to apply the probe with light pressure by monitoring the real-time image to obtain continuous images that are appropriate for elasticity analysis. Availability of automated pressure applier should help to reduce the difficulty of applying TRTE and to create stable and reproducible images.

The ideal imaging technique should be affordable and minimally invasive, with little variability in interobserver interpretation. In our study we used a commercially available ultrasound machine and probe. The internally loaded hardware has enough capacity of memory to record the entire procedure, and the examiner can recall the recorded images at any time after the examination. The necessary compression force toward the prostate was minimal and there were no incomplete examinations according to the discomfort or pain reported by patients. Furthermore, our study demonstrated that the interobserver variability of TRTE was better than TRUS and comparable to PDUS by using a newly adopted scoring system.

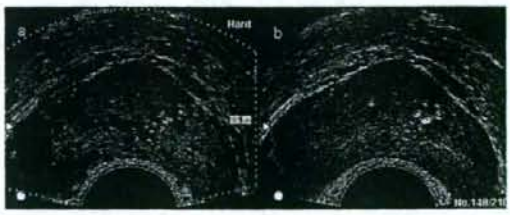

Fig. 4. Example of false-positive elastography findings in the chronic prostatitis patient. There was a slightly hypoechoic lesion without clear boundary in the right peripheral zone at the B-mode image (b). The elastography image (a) showed the focal asymmetric lesion in blue with mosaic patternlike appearance (elastography score 3). Biopsy core from the right peripheral zone was histologically confirmed with chronic prostatitis.

In addition, the ideal test should be able to predict tumor stage, volume, and location with high specificity and sensitivity. Unfortunately, none of the previous studies, including ours, demonstrated the relationship between TRTE findings and pathologic tumor stage. To evaluate the ability of TRTE to predict tumor stage, volume and location, a prospective study is necessary to compare the preoperative TRTE findings and final pathologic finding in radical prostatectomy specimens.

CONCLUSIONS

TRTE is a feasible technique for detecting prostate cancer, which achieves a comparable sensitivity to PDUS. We believe that elastography can complement conventional ultrasound, thereby making it easier to diagnose prostatic lesions. Elastography is promising, and we expect that this imaging modality will become an invaluable tool for the diagnosis of prostatic diseases in the clinical setting.

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Real-time virtual ultrasonographic radiofrequency ablation of renal cell carcinoma

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Study Type – Diagnostic (exploratory cohort study)
Level of Evidence 2b

OBJECTIVE

To evaluate the usefulness of real-time virtual ultrasonography (RVS) as a new navigational tool for percutaneous radiofrequency ablation (RFA) of solid renal cell carcinoma (RCC).

PATIENTS AND METHODS

Ten patients with 13 RCCs were treated with percutaneous RFA using RVS, which displays ultrasonograms and corresponding multiplanar reconstruction images of computed tomography in parallel.

RESULTS

RVS allowed excellent anatomical visualization and precise navigation of RFA for RCC. All patients were treated successfully in one session with percutaneous RVS RFA. There were no significant complications, and none of the patients had a local tumour recurrence during the follow-up.

CONCLUSION

RVS for RFA of solid RCC is a new and promising alternative imaging method.

KEYWORDS

ablation, RCC, kidney, radiofrequency, imaging

INTRODUCTION

The estimated worldwide incidence of RCC is 150 000 cases, constituting ≈2% of malignancies in adults [1]. Solid renal masses are being detected more frequently with the increased use of cross-sectional imaging [2]; of RCCs, 25–49% are now detected incidentally [3]. Independent of the improved detection of RCC, a rise in incidence was registered in Western industrialized countries [4]. The treatment for solid malignant renal masses is open or laparoscopic nephrectomy, or partial nephrectomy [5]. These procedures are invasive, require hospital admission, general anaesthesia, and operating room time, along with their attendant risks and costs.

Percutaneous radiofrequency ablation (RFA) is a palliative alternative in patients who are poor candidates for surgical resection due to comorbidities [6]. In percutaneous RFA, an applicator is placed into the tumour using imaging guidance, and thermal energy is applied to the tumour, leading to cell death. RFA is a minimally invasive technique that can effectively be used for local tumour control, preserving healthy renal parenchyma, reducing the overall morbidity of surgery, allowing earlier hospital discharge and faster convalescence, and decreasing overall healthcare costs [7,8].

The percutaneous needle has been placed for RFA therapy, and treatment monitored, using ultrasonography (US), fluoroscopy, CT or MRI guidance [3,9–11]. US allows the body to be scanned from various positions and angles. The images generated by conventional cross-sectional images (CT/MRI) are displayed as horizontal tomographic slices. Clinicians must synthesise mentally a three-dimensional model of the body from many two-dimensional horizontal images.

Real-time virtual US (RVS, Hitachi Medical Corporation, Japan) is a new technology that allows the fusion of real-time US and preoperative CT data. RVS displays the synchronised pictures of both real-time US and CT in the same section of the body, simultaneously.

In the present study we evaluated the usefulness of percutaneous RFA under RVS guidance for RCC, with the aim of assessing whether RVS could achieve precise needle placement and thus potentially reduce radiation exposure compared to conventional CT-guided needle placement.

PATIENTS AND METHODS

The present study included 10 patients (eight men and two women, who fulfilled four selection criteria: they had localized renal

*FIG. 1. Imaging from a 77-year-old man with diabetes mellitus and chronic renal insufficiency (serum creatinine 1.4 mg/dL) and prostate cancer undergoing hormonal treatment. The main complaint was a tumour in the left kidney, a 2.2 × 1.7 cm enhancing mass. The exophytic posterior mass is shown. Biopsy confirmed a clear-cell RCC. **a**, preoperative CT image showing the lesion; **b**, synchronized imaging of the kidney with RVS; **c**, guidance of renal puncture using RVS.*

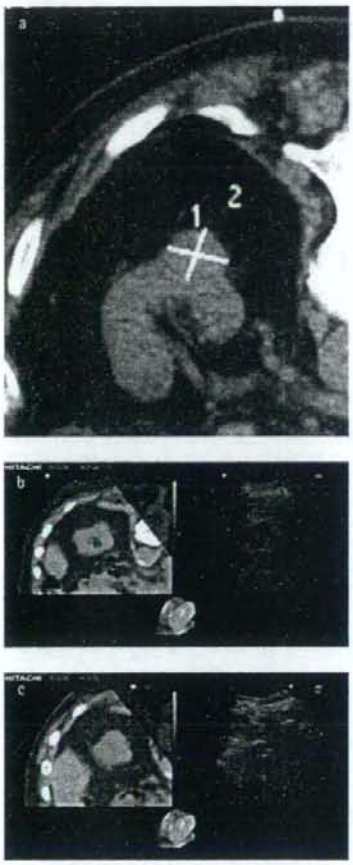
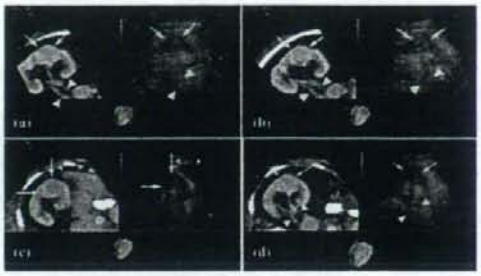


FIG. 2. Synchronised CT and RVS in continuous scanning from various angled manipulations of the ultrasound probe. The patient had a posterior 35-mm enhanced renal tumour (arrows). The reconstructed CT image helps to depict the artery and vein in the renal hilum (arrow heads in A, B and D), the ultrasonograms of which were difficult to interpret without RVS assistance. The combined interpretation of the RVS and synchronised CT image provides a better anatomical interpretation of the perinephric anatomy, e.g. the edge of liver (small arrow heads in C), which should be avoided by the puncture line for needle guidance.



tumours of <4 cm; they were elderly and/or a poor surgical risk, or had had previous ipsilateral kidney surgery; or had multiple tumours in the same kidney; or had compromised renal function.

All patients initially had CT and thereafter RVS-guided RFA therapy; MRI was used during the follow-up. Informed consent was obtained from all subjects.

The patient was assessed while supine using a CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Germany). Contrast medium was injected i.v. and four-phase CT scans taken, with the scanning parameters being: 0.625 mm collimation × 16; table speed 6 mm/s (pitch, 1.75); 350–400 mA; 120 kV; 512 × 512 matrix. Transverse images were reconstructed at 0.625 mm intervals with a 0.625-mm section overlap. All CT data were transferred to the US system.

The RVS system comprises an ultrasound scanner, a magnetic probe motion-tracking device and a personal computer. First, the previously acquired CT volume data were loaded onto the US system. Patients were placed supine with shoulders, buttocks and heels in contact with the table. Water-soluble transmission gel was applied to the 3.5 MHz transducer. During real-time US the ultrasound machine generates multiplanar reconstruction (MPR) images from the CT volume data, corresponding to the US images of the same cross-section side-by-side. The RVS image was reconstructed as an optimally angled plane from the CT slice data. To align the RVS image and the conventional US image, two or three different organs of the tumour, renal artery and renal vein were used as fiducial landmarks. Then, a real-time display of the MPR images that corresponded to the US cross-sectional images was shown next to the US cross-sectional images on the same monitor screen.

Several issues when using RVS for kidney imaging are relevant. First, the CT dataset should be obtained in the same position as the percutaneous procedure, to eliminate organ movement with body repositioning. Second, the CT dataset should also be obtained within a normal breath-hold, to minimize respiratory movement (if under local anaesthesia) and to minimize the discrepancy of synchronization between RVS and the CT dataset.

Before RFA treatment, 15 mg of pentazocine hydrochloride and 25 mg of hydroxyzine hydrochloride were administered i.m. During RVS the puncture needle was visualized as a hyperechoic silhouette on the monitor, and the needle was advanced to the target site. A 17-G Cool-Tip electrode with a 2-cm exposed metallic tip (Radionics, Burlington, MA, USA) was introduced via the puncture needle to the target site; a 480-kHz monopolar radiofrequency generator was used.

RESULTS

The study included 10 patients (eight men and two women; mean age 73 years, range 67–89), with 13 renal lesions, all confirmed as solid RCC on biopsy. One patient had a renal transplant graft. The mean (range) tumour diameter was 2.8 (1.0–4) cm. Of the 13 lesions, seven were in the right kidney, five in the left and one in a renal transplant graft. All tumours were visualized on CT/RVS and in all patients there were no problems with the imaging.

For RFA the whole abdominal area was scanned using RVS. Reconstructing slices from various angles was not a problem. Each slice was continuously animated, as in conventional US. The shape of the kidney and

*FIG. 3. Imaging from a 57-year-old man with diabetes mellitus and chronic renal insufficiency (serum creatinine 1.7 mg/dL), hypertension and renal artery stenosis with a renal stent. There is a tumour in the left-kidney (2.0 × 1.7 cm enhancing mass) exophytic on the postero-mid segment (**a**). Biopsy confirmed papillary RCC. **b**, synchronised RVS; **c**, At the 6-month follow-up by MRI there was no enhancement.*

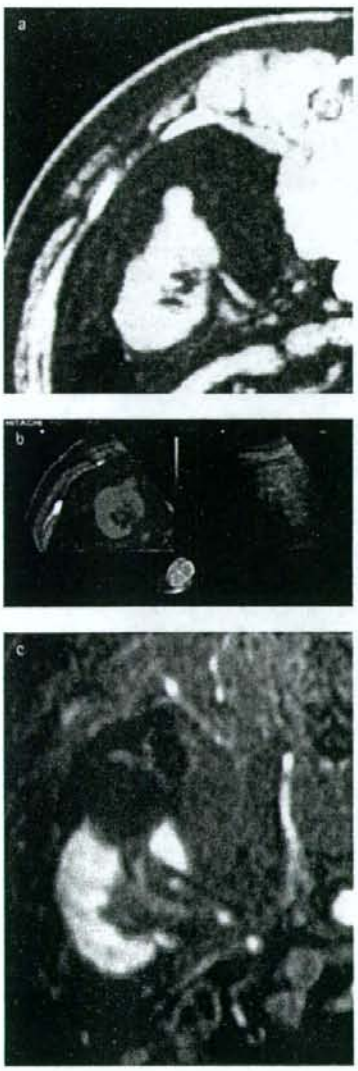
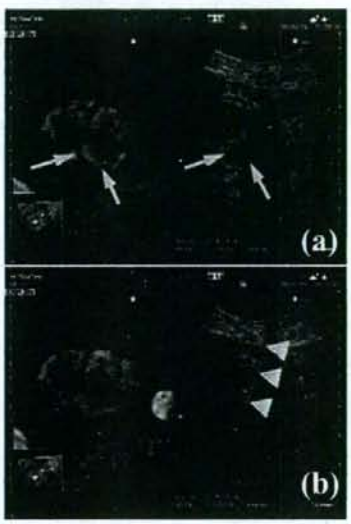


FIG. 4. A patients with centrally enhanced residual renal tumour (arrows) after previous radiofrequency treatment. RVS was used during surgery to monitor the completion of needle advancement into the enhanced lesion (arrow heads). Without the aid of the reconstructed enhanced MRI image, it is almost impossible to identify centrally located enhanced residual renal tumour with US alone. Only with the combination of RVS targeting of the centre of the enhanced lesion could this be achieved.



the surrounding organs indicated that the slices identified by CT and US were identical. RVS images could be constructed for all lesions, and RFA was successful in all patients in one treatment session, with complete necrosis obtained in all. For RFA, there were mild complications of pain and fever, but no severe complications. In none of the patients was there local tumour recurrence during the follow-up.

In a representative case (a 77-year-old man) of RFA, the lesion was in the left kidney. An RVS-guided puncture of the target area was made (Fig. 1) and after treatment, MRI showed accurate ablation of the target site. Further representative cases are shown in Figs 2–4.

DISCUSSION

Percutaneous RFA could offer a minimally invasive treatment for elderly patients not suitable for general anaesthesia. RFA can preserve more healthy renal parenchyma, with no significant blood loss, than can nephron-sparing surgery, and therefore be an alternative to conventional surgery in patients with reduced renal function or multiple RCCs [1,6–8,12]. However, a clinical trial comparing long-term renal function after RFA and nephron-sparing surgery has not yet been reported [13].

As tumour size is a strong predictor of the outcome of ablation, small tumours (<4 cm) seem to be the most appropriate indication for RFA. These tumours can be technically successfully treated in 92–100% of cases with one or several sessions using commercially available RF ablation systems under CT guidance [3,5,11,14]. Complete ablation will typically require one treatment session in tumours of <3 cm. Complete ablation was also reported for tumours up to 5.5 cm in diameter, which requires many applicator re-positionings and subsequently longer treatment times. Tumour location seems to be a further predictor of the success of RFA [15]. Exophytic tumours, which according to the definition invade the perirenal fat, are easier to puncture than are more central tumours. The insulating effect of the fat capsule allows for higher ablation temperatures, whereas blood flow in the large hilar blood vessels causes a cooling effect.

Imaging guidance in RFA, and treatment monitoring, can be done using US, CT or MRI [3,5]. The abdominal area is complex, and includes numerous organs and vessels that make understanding the structure of the abdomen difficult on US. Conventional US allows slices across the whole abdominal area to be scanned from various positions and angles. The US B-mode method is suitable for detecting renal lesions, and thus RFA therapy for RCC has been done under US guidance [16]. However, US seems to be the least favourable of the methods for RFA, as bubbles produced by the vaporization during the procedure significantly disturb the image quality due to their hyper-echogenicity. With conventional US it has also been difficult to determine the residual viable portion of RCC after treatment, because of the similar appearances of necrosis and viable tumour tissue. Therefore, reliable monitoring of RFA is not yet feasible with US. No significant changes in the imaging pattern of the ablated renal masses are detectable on CT [17]. Residual tumour tissue can be detected by CT after administering a contrast medium, because the tumour tissue generally shows signal enhancement, whereas the coagulation necrosis does not. Contrast medium can only be injected once for each RFA session, as the contrast medium might need several hours to clear. The need for up to four treatment

sessions was reported for CT guidance to achieve complete tumour necrosis [12]. Furthermore, some RCCs show no contrast enhancement and therefore contrast-enhanced CT does not allow monitoring of the RFA. As stated, CT must normally be used several times during therapy by conventional means, and comparing images from US and CT is often difficult [3]. In the present study we used CT only once before RFA; using the present RVS system the agreement between US and CT images was confirmed. RVS is also useful for treating lesions that cannot be visualized on US but are apparent on CT. A lesion detected by RVS can readily be placed by conventional US using the surrounding anatomical relationships. Furthermore, RVS is useful in RFA [18,19]; as lesions after RFA show a very irregular area, and target lesions can be difficult to identify, treatment is often complicated by the need for additional sessions after the initial session of RFA. Such lesions can reportedly be treated using contrast-enhanced US [20–23], but this method is very difficult and not all lesions are contrast-enhanced. In such cases, RVS showing both US and CT simultaneously should facilitate the treatment.

MRI was suggested for applicator navigation and treatment monitoring in several studies [3,10,24]. MRI is optimally suited for imaging guidance in RFA due to its intrinsically high soft-tissue contrast, the capability of true multiplanar imaging due to the free choice of the applied imaging gradients, and the possibility of applicator targeting with sequences of MR fluoroscopy. MRI is the only method providing near on-line monitoring of the ablation procedure. Changes after RFA are visible in T2-weighted MRI; tumour ablation is apparent in areas of signal loss in T2-weighted imaging, replacing the isointense or hyperintense signal of the RCC. Residual tumour tissue can be detected by its persisting isointense or hyperintense signal. The applicator can be repositioned to the area of incomplete treatment, and a further ablation cycle delivered. RFA allows an indefinite number of subsequent ablation cycles, and the repeated assessment of ablation outcome, with no new injection of contrast media, thus providing a major advantage of MRI. The reported success rate for complete tumour ablation was 92–100% of cases within one session for MR guidance [3,10,24]. However, MRI is expensive, not yet universally available and the imaging procedure is long.

In future, RVS of the kidney will be available for any renal-puncture procedures, e.g. percutaneous nephrostomy, renal tumour biopsy, renal tumour cryosurgery or for intraoperative laparoscopic US. In the present study the RCC lesions were found and punctured using only one session. The needle was advanced with complete accuracy to all target lesions, indicating that RVS has good efficacy. The RVS image showed an adequate site for puncture, and thus RVS RFA was used significantly fewer times than in reported standard RFA. Therefore, the length of hospital stay, number of CT examinations required to estimate therapeutic efficacy, and the cost are expected to decrease with use of this system.

Thus the present US and CT-fusion system, RVS, is helpful for guiding percutaneous RFA for kidney tumours, with a significantly less radiation exposure than CT-guidance alone. Further studies are needed to evaluate the clinical utility of RVS for precise needle placement and monitoring. There were no local recurrences after RVS RFA, and no major complications in any patients, indicating that the treatment is safe. In conclusion, RVS is useful for visualizing RCC and greatly assists RFA treatment, by better anatomical orientation and therefore better navigation.

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Abbreviations: **RFA**, radiofrequency ablation; **US**, ultrasonography; **RVS**, real-time virtual US; **MPR**, multiplanar reconstruction.

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Original Article: Clinical Investigation

Prospective study of combined treatment with interferon-alpha and active vitamin D_3 for Japanese patients with metastatic renal cell carcinoma

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Objectives: To assess the safety and efficacy of combined therapy with interferon-alpha (INF-α) and active vitamin D_3 for metastatic renal cell carcinoma (RCC).

Methods: Sixteen patients with metastatic RCC were enrolled in this prospective study. All received oral alfacalcidol (1 μg once daily) and INF-α (Sumiferon; 3 million units, three times a week). The primary endpoint was the response rate (defined as complete + partial remission). Secondary endpoints were cancer-specific survival and toxicity. The median follow-up period was 17 months (range: 5–49 months).

Results: The median age of the patients was 68 years (range: 41–73 years). The sites of metastases were: lung in 13 patients, bone in one, lung and bone in one, and lung, bone, and lymph nodes in one. Four patients (25%) had a partial response (PR), 10 patients (62.5%) showed no change (NC), and two patients (12.5%) had progressive disease (PD). The median cancer-specific survival time was 45 months. One patient had to discontinue vitamin D_3 because of hypercalcemia. Kaplan-Meier survival analysis revealed that metastasis at the time of initial diagnosis and older than average age were significant predictors of poor survival ($P < 0.05$).

Conclusions: Combined treatment with INF-α and active vitamin D_3 has shown to be safe and effective for metastatic RCC patients.

Key words: active vitamin D_3, combined immunotherapy, metastatic renal cell carcinoma.

Introduction

Advances in understanding the biology and genetics of renal cell carcinoma (RCC) have led to several novel approaches to the treatment of metastatic RCC.[1] Recently, two targeting agents (sorafenib and sunitinib) were approved by the US Food and Drug Administration for the treatment of advanced RCC.[1] Until recently, interleukin-2 (IL-2) and interferon-alpha (IFN-α) produced objective responses in 10–15% of patients with RCC.[2] IFN-α, the comparator for many trials in RCC, achieves a median progression-free survival of nearly 5 months and a median survival of 12 months.[3] These observations suggest that urologists should establish combined treatment with IFN-α that shows antitumor synergism.

The active form of vitamin D, 1α, 25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), is widely recognized to inhibit cell proliferation and induce the differentiation and apoptosis of some malignant tumors, in addition to its role in calcium metabolism.[4] Several groups have provided epidemiological evidence that reduced availability of sunlight is correlated with an increased incidence of carcinoma of the breast, colon, and prostate, possibly due to the lack of vitamin D production.[5] We previously reported that the serum level of $1,25(OH)_2D_3$ was significantly lower in patients with RCC compared with healthy controls in a Japanese population.[6] Moreover, we have demonstrated that $1,25(OH)_2D_3$ inhibits the growth of mouse renal cell carcinoma (RENCA), partly through the inhibition of angiogenesis.[7] It is known that $1,25(OH)_2D_3$ exerts its activity through the intracellular vitamin D receptor (VDR), which forms a heterodimer with the retinoid X receptor. The heterodimer in turn binds to vitamin D response elements in the promoter regions of target genes to regulate the transcription of those genes (e.g. the p21 gene).[8] At the cellular level, stimulation of VDR and retinoid receptors can lead to the inhibition of cell proliferation and angiogenesis, as well as to the induction of differentiation and apoptosis.[9] These results suggest that the vitamin D-VDR system is related to the development of RCC.

It has been widely recognized that the mechanism by which IFN-α acts on RCC involves activation of immunocytes such as natural killer cells and phagocytic cells, a direct antitumor effect on cancer cells, upregulation of antigens to cancer cells such as major histocompatibility complex (MHC) class I molecules, and induction of apoptosis.[10] The $1,25(OH)_2D_3$ has antitumor effects such as promotion of cell cycle arrest in G1 through upregulation of WAF1 and KIP1 and downregulation of cyclin D1, as well as induction of apoptosis through upregulation of BAK, BAX, and caspase 3 and downregulation of Bcl2 and IAP.[4] Based on these findings, combined treatment with IFN-α and active vitamin D_3 could have potential antitumor activity against RCC.

The purpose of the present study was to determine whether combined therapy with IFN-α and active vitamin D_3 was superior to IFN-α alone in Japanese patients with metastatic RCC.

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Methods

From July 2001 to November 2006,the subjects were patients hospitalized at the eleven medical institutions that met the following selection criteria and gave informed consent to participate in the study after receiving a thorough explanation. The selection criteria were: (i) patients with progressive renal cell carcinoma in Stage IV (2002 TNM classification) who had an evaluable metastatic focus and a histologically confirmed diagnosis of renal cell carcinoma; (ii) patients who had undergone radical nephrectomy and had not received any prior treatment for the metastasis after surgery; (iii) patients who had adequate function of their bone marrow, liver, kidneys, heart, and lungs; (iv) patients without hypercalcemia; (v) patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and (vi) patients aged ≥20 and <75 years. The following exclusion criteria were also used: (i) patients with brain metastasis; (ii) patients with hypersensitivity to IFN-α preparations or active vitamin D_3 preparations; (iii) patients with hypersensitivity to biological preparations such as vaccines, etc.; (iv) patients taking Sho-saiko-to (a Chinese herbal medicine); (v) patients with autoimmune hepatitis; (vi) patients already receiving IFN-α preparations or active vitamin D_3 preparations; (vii) patients using calcium preparations; (viii) pregnant or breastfeeding women, as well as those who might be pregnant or those who intend to become pregnant; (ix) patients with other serious complications; and (x) other patients who were judged by the attending physician to be ineligible for the present study. This study was carried out with approval from the ethical committee of each institute.

Interferon-α (Sumiferon) and alfacalcidol (Alpharol) were given together for at least 3 months. Thereafter, these drugs were given for up to 3 years until the detection of tumor progression (PD). IFN-α was injected intramuscularly three times a week at a dose of 300 million units, while alfacalcidol was given orally in a once daily dose of 1 μg.

The first evaluation of tumor response was assessed after 4–12 weeks, and then an evaluation of tumor response was carried out every 12 weeks. The patients received combined treatment until progression of the disease. Response criteria were used according to the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan (Japanese Urological Association 1999). A complete response (CR) was defined as the disappearance of all measurable lesions. A partial response (PR) was defined as at least a 50% decrease from the baseline in the sum of the products of the diameters of the measurable lesions without evidence of new lesions. Progressive disease (PD) was defined as at least 25% increase in the area of the measurable lesions, or the appearance of new lesions. No change (NC) was defined as the absence of a complete or partial response, or progression.

Adverse events were assessed on the basis of the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

The primary endpoint was the response rate, and the secondary endpoint was the survival rate. Regarding statistical analysis, the survival rate was calculated according to the Kaplan-Meier method, and intergroup comparison was done by the log-rank test. SPSS (ver 14.0 J) was used for the analysis, with $P < 0.05$ indicating significance.

Results

Twenty patients were registered in the present study. Of these patients, one did not attend hospital after registration (ineligible patient), but the other 19 patients were eligible. In addition, one patient died of cancer at 1 month after registration, one patient discontinued treatment 1 month after the start of administration due to adverse drug reactions, and one patient received transarterial embolization (TAE) 3 months before evaluation, so these three patients were also excluded (discontinued/withdrawn patients). Therefore, 16 patients were available for the assessment of efficacy. The characteristics of these 16 patients are shown in Table 1. Thirteen patients were men and three were women, with a median age of 68 years (range: 41 to 73 years; mean age: 63.8 years). Metastases involved the lung in 13 patients, the bone in one, lung and bone in one, and lung, bone, and lymph nodes in one. The median treatment period was 7.0 months (range: 3 to 26 months).

Table 1 Characteristics of the patients assessed for efficacy ($n = 16$)

Item		No. patients
Sex	M	13
	F	3
Age	Median	68 (years)
	Range	41–73 (years)
Tumor size	pT1	9
	pT2	1
	pT3	6
Lymph node status	pN0	10
	pN1 or pN2	2
	pNX	4
Grade	G1	1
	G2	9
	G3	2
	Gmix	4
Histology	Clear cell	13
	Granular cell	2
	Spindle cell	1
Venous invasion	–	6
	+	7
	Unknown	3
Distant metastasis	M0	8
	M1	8
Site of metastasis†	Lung	13
	Bone	1
	Lung + bone	1
	Lung + bone + lymph node	1
Performance status†	0	9
	1	7

†Data on registration. Tumor stage according to TNM. Tumor grade according to the 2002 American Joint Committee on Cancer (AJCC) grading system. Performance status according to the Eastern Cooperative Oncology Group (ECOG).

Eligible patients (19) were followed up for 1 to 52 months (median: 17.0 months). The 16 patients subjected to assessment of efficacy were observed to determine the effect of combined treatment with IFN-αand alfacalcidol for a period of 5 to 47 months (median: 17.0 months). The median overall survival time was 45.0 months (range: 5 to 47 months) and the median cancer-specific survival time was 45.0 months (range: 5 to 47 months) (Fig. 1). The outcome was partial response (PR) in four patients (25%), no change (NC) in 10 patients (62.5%), and progressive disease (PD) in two patients (12.5%) (Table 2).The mean duration of PR in the responding patients was 3.2 months, and the median response time was 3 months. The characteristics of the patients (PR) for whom the combined treatment was effective are shown in Table 3. The PR patients included those with multiple metastases (lung, bone, and

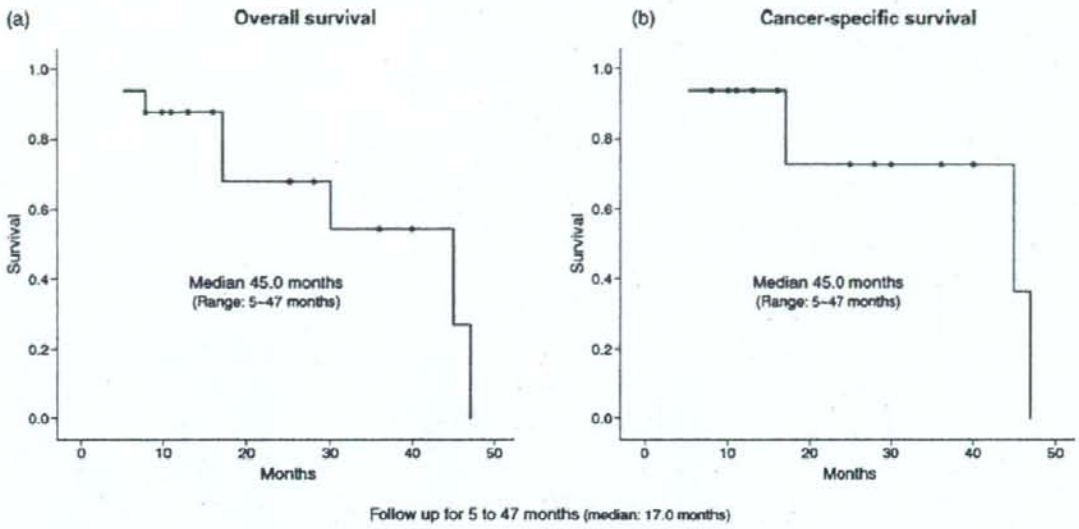

Fig. 1 Survival curves for patients subjected to assessment of efficacy ($n = 16$). Patients subjected to assessment of efficacy were followed for 5–47 months. The median survival time was 45.0 months and the median disease-specific survival time was 45.0 months.

Table 2 Response to combined treatment with interferon-alpha (IFN-α) and alfacalcidol in 16 patients subjected to assessment

Response	CR	PR	NC	PD	Total
No. patients	0	4	10	2	16
Percentage (%)	0	25.0	62.5	12.5	100

CR, complete response; NC, no change; PD, progressive disease; PR, partial response.

lymph nodes), for whom treatment was difficult, and those with spindle cell carcinoma, which is a type of cancer with a poor prognosis, suggesting that the combination of IFN-α and alfacalcidol was effective. Figure 2 shows a bone scintigram and computed tomography (CT) scan from a PR patient. This patient was found to have metastases to the lung and bone at 5 months after nephrectomy and therefore was registered in the present study. The patient received combined treatment at 13 days after registration. Bone scintigraphy carried out at 11 months after treatment revealed the disappearance of a site of increased uptake suggesting metastasis to the bone, whereas the chest CT scan obtained 14 months after treatment revealed the disappearance of an opacity suggesting metastasis to the right lung. This patient died from RCC progression 46 months after combined treatment.

There were no clear differences of histopathological classification, site of metastasis, prognostic factors of Motzer (performance status [PS], lactate dehydrogenase [LDH], hemoglobin, corrected Ca, and nephrectomy) between PR patients and PD patients who received combined treatment with IFN-α and alfacalcidol. Further, the median survival time without progression was 7.0 months (range: 3 to 26 months) (Fig. 3).

Among the patients subjected to assessment of efficacy (16), those who had metastasis at the time of nephrectomy (M1) showed a significantly worse prognosis in terms of both overall survival ($P = 0.034$) and cancer-specific survival ($P = 0.022$) compared with the patients who did not have metastasis (M0) (Fig. 4a). Further, the patients whose age at the start of the study was lower than the mean age (63.8 years) had a significantly worse prognosis in terms of cancer-specific survival ($P = 0.033$) compared with the patients whose age at the start of the study was higher than the mean (Fig. 4b).

Grade 3 or 4 adverse drug reactions occurred in four out of 19 patients (21%) (Table 4). The reactions were atrial fibrillation, decreased white blood cell count, hypercalcemia, and delirium. All four patients discontinued their treatment. The remaining 15 patients only had mild adverse drug reactions, and were able to continue their treatment.

Discussion

It has been reported that the vitamin D and its analogs have an antitumor effect against various malignancies.[5] It has been demonstrated that vitamin D deficiency and insufficiency are under-recognized problems worldwide, and are associated with a higher prevalence and unfavorable course of cancer. Recent investigations have analyzed the molecular mechanisms that underlie genomic and nongenomic vitamin D signaling pathways and their importance in terms of the antitumor effect of vitamin D analogs. It has been shown that a multitude of independent molecular events, including effects on cell proliferation, differentiation, apoptosis, and DNA repair, are related to the antitumor activity of vitamin D.[11]

In this study, the subjects were all patients who had undergone nephrectomy. The response rate was 25.0% (4/16) and the median cancer-specific survival time was 45 months after a maximum follow-up period of 52 months, which were relatively better response and survival data than obtained in previous reliable studies such as SWOG 8949[12] and EORTC 30947[13]. Because 15 patients had metastatic lesions of less than 3 cm, this may have improved the results. Our

Table 3 Characteristics of patients achieving PR on treatment with interferon-alpha (IFN-α) and alfacalcidol

	Sex	Age	Metastases	pT	pN	M	V	Grade	Histology	PR period
1	Male	55	Lung	1a	0	1	(+)	G3	Spindle cell	2 months
2	Male	74	Lung, bone, lymph nodes	1b	0	0	Unknown	G2	Clear cell	3 months
3	Male	61	Lung	3b	0	0	(+)	G2	Clear cell	3 months
4	Male	68	Lung	3a	X	X	(+)	G2	Clear cell	6 months

M, distant metastasis; pN, lymph node status; PR, partial response; pT, tumor size; v, venous invasion.

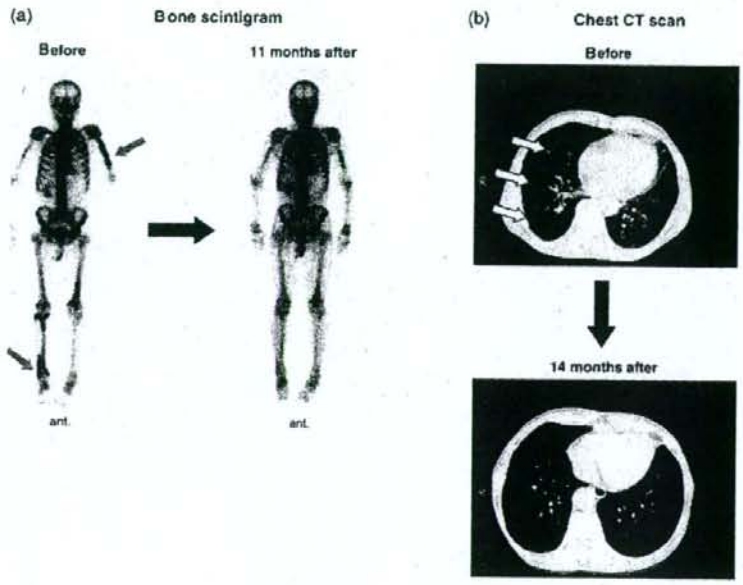

Fig. 2 Clinical course of partial response (PR) case. (a) Bone schintigram revealed that increased uptake was found before combined treatment with interferon-alpha (IFN-α) and alfacalcidol, and this disappeared at 11 months after treatment. (b) Computed tomography (CT) showed metastasis of the right lung was found before combined treatment, and this disappeared at 14 months after treatment.

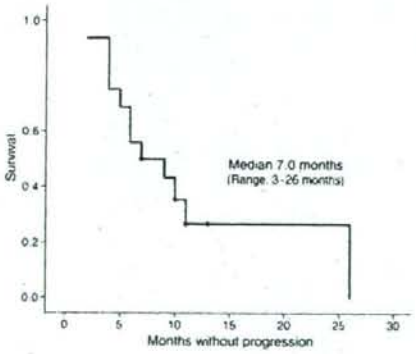

Fig. 3 Non-progression survival of the patients ($n = 16$). The median non-progression survival time was 7.0 months (range: 3–26 months).

PR cases included multiple metastases (lungs, bone, and lymph nodes) and spindle cell cancer that usually has a poor prognosis. The reason why these cases showed a response is unclear, but there was a possibility that it was due to synergism between vitamin D and INF-α. The results of the present study suggested that this combined therapy may prolong the survival of patients with metastatic RCC.

Patients who had metastasis at nephrectomy showed significantly worse prognosis compared with those who did not have metastasis, both for overall survival and cancer-specific survival. In addition, the patients with a lower than average age at the start of the study had a significantly worse prognosis compared with those having a higher than average age (cancer-specific survival). The reason why younger patients showed a poor prognosis is unclear. In order to confirm these results, a prospective randomized study enrolling a large number of subjects will need to be carried out.

The dosage of INF-α for advanced RCC has not yet been well defined. Atkins reported that thrice-weekly doses in the 5–10 MU/m^2 range had the highest therapeutic index, although no clear dose-response relationship exists.[14] In the present study, natural INF-α was given at 3 MU/day of Sumiferon 3 days a week. Recent prospective clinical trials[15] have involved the use of INF-α daily starting at a dose of 3 MU. The dose was escalated every 7 days from 3 to 9 MU in increments of 3 MU, although there is no established administration method in Japan. To augment the efficacy of INF-α, use in combinations with other biological response modifiers or chemotherapy agents has been tried. A randomized phase III study comparing 13-cis-retinoic acid plus recombinant INF-α with recombinant INF-α alone for

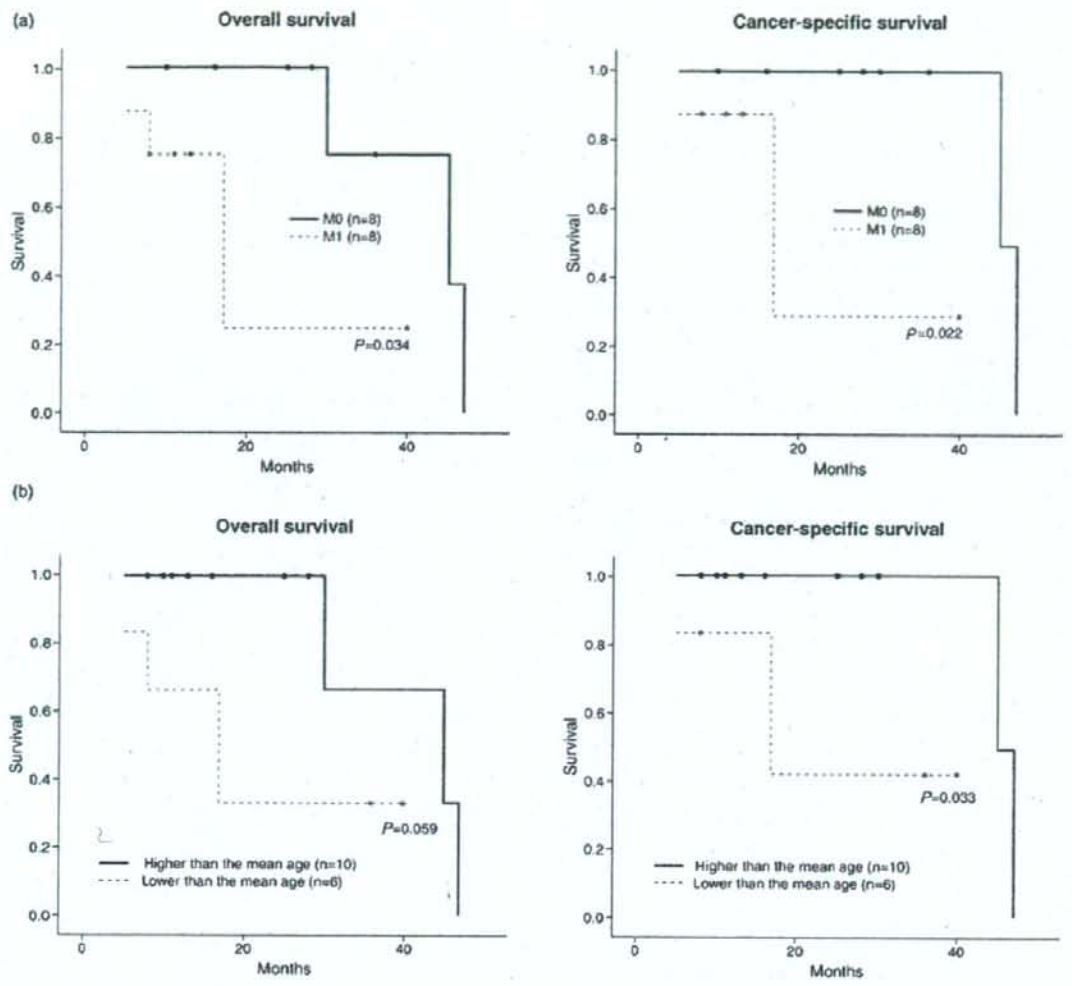

Fig. 4 Survival and cancer-specific survival of patients. (a) Relation to the presence or absence of metastasis at the time of nephrectomy. The patients who had metastasis at the time of nephrectomy showed a significantly worse prognosis both overall survival (OS) ($P = 0.034$) and disease-specific survival (DSS) ($P = 0.022$) compared with the patients who did not have metastasis (a). (b) Relation to the patient's age. The patient's age was lower than the mean age, and had a significantly worse prognosis in terms of DSS compared with those whose age was higher than the mean age ($P = 0.033$) (b).

Table 4 Patients with Grade 3–4 adverse drug reactions

	Age	Sex	Adverse event†	Grade†	Outcome
1	54	Male	Atrial fibrillation	4	Reduced after treatment
2	68	Male	Decreased white blood cell count	3	Recovery after discontinuation
3	44	Male	Hypercalcemia	4	Recovery after discontinuation and medication
4	73	Male	Delirium	3	Improved after discontinuation

†CTCAE (Common Terminology Criteria for Adverse Events) v3.0.

advanced RCC demonstrated that progression-free survival and overall survival were significantly longer with recombinant INF-α plus 13-cis-retinoic acid than with recombinant INF-α alone.[15]

Adverse events experienced in the present study were primarily related to INF-α, such as leukopenia and atrial fibrillation. The latter symptom was detected by this study for the first time as a side effect of IFN-α. Although one patient had to discontinue active vitamin D because of hypercalcemia (grade 3), this was improved after withdrawal of the drug. There have been several reports relating to the safety and efficacy of vitamin D analogs for treatment of various malignancies.[16,17] These clinical studies have demonstrated that such analogs show promise for cancer therapy, at least for palliative treatment, and are synergistic in combination with cisplatin, docetaxel, or other agents.

In conclusion, this study showed that combined treatment with interferon-alpha and active vitamin D_3 had potential antitumor activity without causing severe adverse events in Japanese patients with metastatic RCC. Recently, molecular-targeting drugs have been developed for the treatment of RCC, and better results have been obtained than with conventional cytokine treatment in Europe and the USA. In the future, it will be necessary to establish the appropriate use of novel molecular-targeting therapy or combination therapy with IFN-α and other antitumor drugs, including vitamin D, as well as the concomitant use of these novel drugs with IFN-α and other agents.

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Original Article: Clinical Investigation

Ten year trend in prostate cancer screening with high prostate-specific antigen exposure rate in Japan

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Background: The tendency of the results and quality control of prostate cancer screening serially performed for 10 years in an area of Japan were evaluated.

Methods: A total of 39 213 men over 55 years of age have participated in the mass screening of prostate cancer in the Otokuni District, since 1995. Men whose prostate-specific antigen (PSA) levels were more than 4.1 ng/mL were indicated for the second screening. In the second screening, prostate-specific antigen density (PSAD) was calculated in men whose PSA levels ranged from 4.1 to 10.0 ng/mL.

Results: Secondary screening was indicated in a total of 2428 subjects, of whom 1633 underwent it. Prostate cancer was diagnosed in 267 men. As a result of the evaluation of the indication of prostate biopsy according to the PSAD in 894 who underwent secondary screening for the first time, the procedure was judged to be unnecessary in 269 (35%) of 765 cases. Of these 269 subjects, 23 (8.5%) were found to have cancer. Clinically localized prostate cancer increased by 17%, and locally advanced and metastatic cancers decreased by 12% in the second compared with the first five years of the ten-year period. The exposure rate of PSA screening in the Otokuni District was 65% with the application for the rate of screenees whose PSA level was 4.1 ng/mL or above.

Conclusions: The Japanese basic health screening system allows the determination of high-PSA exposure areas. Serial prostate cancer screening showed a tendency of stage migration in the screened cancer patients. The use of PSAD in secondary screening substantially reduces the necessity of prostate biopsy; however, the encouragement of PSA-positive individuals to periodically receive prostate cancer screening is essential to maintain the quality of the screening system.

Key words: Prostate cancer, PSA, screening, PSA density

Introduction

The incidence of and mortality from prostate cancer in Japan is still lower than it is in Western countries.[1] However, prostate cancer is becoming a major public health concern in Japan. The age-adjusted incidence of this malignancy rapidly increased 6.5 times between 1975 and 1998.[2] In addition, the age-adjusted mortality rate also increased 4.3 times between 1980 and 2000.

In conjunction with the recent rapid increases in the incidence of and mortality from prostate cancer in Japan, the percentage of local governments providing prostate cancer screening increased five times during the six years following 2000 (14.7% in 2000, 71.2% in 2006).[3] This rapid increase in the number of local governments that started prostate cancer screening reflects the recent increase in concern over prostate cancer among the Japanese.

In Japan, the execution of prostate cancer screening is left primarily to local health administrative organizations, university and core hospitals, medical societies mostly consisting of local practitioners, and public or private screening institutions. A survey of such screening facilities in 2006 showed that 87% of them were local health administrative organizations.[3] However, in executing prostate cancer screening in urban areas, the efforts of local health administrative organizations alone are insufficient to efficiently attract primary screenees, and the involvement of general practitioners, most of whom are family physicians, in primary screening is necessary. Also, the designation of core hospitals for secondary screening is necessary for physicians who perform prostate needle biopsy to be able to carry out the detailed management of databases. In Japan, basic health screening consisting of inquiries, body measurements, percussion and auscultation, sphygmomanometry, blood chemistry tests, diabetes tests, and electrocardiogram (ECG) is widely available for people aged 40 years and above as an elderly health protection measure for the promotion of the correct understanding of lifestyle-related diseases and their early detection and treatment.[4] In 1995 in the Otokuni District of Kyoto, we first established a primary prostate cancer screening system in which screenees can freely choose between screening by local governmental administration and individual screening at private medical facilities (primarily local clinics) cooperating in basic health screening. The objectives of this study were to examine Japan's original health screening system and to clarify the characteristics of prostate cancer patients detected by screening using the PSA density (PSAD) as an indicational criterion for prostate biopsy during the past 10 years. In addition, we tried to calculate the exposure rate of PSA screening in the Otokuni District.

Methods

The Otokuni District is located to the south of Kyoto City and consists of two cities and one town (Nagaokakyo City, Muko City, and Oyamazaki Town). It has a population of 147 500 (2004), of which 22 705 (2004) are males aged 55 years and over. The subjects of this study were those who desired screening for prostate cancer among the males aged 55 years and over who have undergone basic health screening in September to October each year since 1995. Primary screening was made by the examination of the serum PSA level alone with a cut-off level of 4.0 ng/mL. The serum PSA level was determined using a Delfia PSA assay kit in all subjects.

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Table 1 Prostate biopsy criteria of second screening

4.1 ≤ PSA ≤ 10	
– DRE-positive or TRUS-positive	Biopsy
– Both DRE and TRUS-negative	
– PSAD > 0.15	Biopsy
– PSAD ≤ 0.15	Recommend to undergo screening next year
PSA ≥ 10.1	Biopsy

DRE, digital rectal examination; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; TRUS, transrectal ultrasonography.

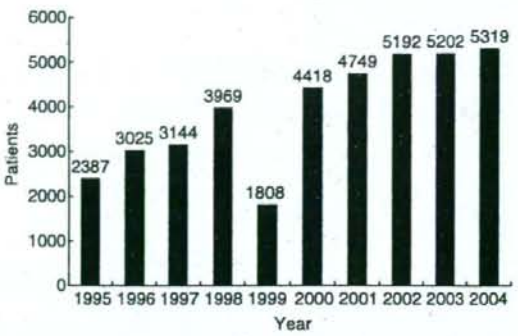

Fig. 1 Annual changes in the number of screenees.

The health administrative organization or private medical facilities in the Otokuni District informed the screenees in whom the serum PSA level was 4.1 ng/mL or above that they should receive secondary screening at a core hospital (Kyoto Saiseikai Hospital). The second screening including prostate biopsy was performed by urologists in Kyoto Saiseikai Hospital using the health insurance system. Table 1 shows the secondary screening system for the selection of candidates for prostate needle biopsy at the core hospital. Biopsy was indicated according to the PSAD, because it was reported to be promising as an indicator of prostate needle biopsy in individuals with a gray-zone PSA level (4.1–10.0 ng/mL) by a study team on the validity of mass screening for prostate cancer (Watanabe Team) under the Ministry of Health and Welfare (presently Ministry of Health, Labor and Welfare).[5]

Digital rectal examination (DRE) was performed by one urologist (K.K) who was a voting member of the Japanese Urological Association. Transrectal ultrasound sonography of the prostate was examined using an ultrasound machine equipped with a chair-type scanner (SSD-520, Aloca, Tokyo, Japan), and the prostate volume was obtained by the step-sectioned method. PSA density was calculated as PSA (ng/mL)/prostate volume (ml).[6] The cut-off value was defined as 0.15.

In men who were indicated for prostate biopsy, transperineal prostate biopsy was undertaken under local anesthesia. The sextant systematic biopsy (SSB) technique was applied between 1995 and 2001. Since 2002, in addition to the SSB technique, an additional sample has been taken from the far lateral region in each lobe. The clinical stage was evaluated according to the TNM system.[7]

Results

Figure 1 shows annual changes in the number of prostate cancer screenees. The number increased more than two-fold in 2004 compared with 1995, when prostate screening was started. In 1999, the number of screenees decreased, because only mass screening was performed; individual screening could not be performed because of the lack of cooperation by the local medical society.

A total of 39 213 people attended primary screening using PSA testing during the 10 years between 1995 and 2004. Of these screenees, 8420 (21%) underwent mass screening at health administration organizations in the Otokuni District, and 30 793 (79%) underwent individual screening at private medical facilities. The serum PSA concentration was 4.1 ng/mL or above in 2428 (6%) of all screenees. Of these screenees, 1633 (67%) received secondary screening, and prostate cancer was detected in 267. Of the 1633 secondary screenees, 1439 (88%) were examined at Kyoto Saiseikai Hospital regarding whether or not they should undergo prostate biopsy. Table 2 shows the percentage of the secondary screenees who underwent biopsy on the basis of their PSA level, the number of biopsies performed and the number of cancers detected (Table 2a: Initial screenees only. Table 2b: All secondary screenees). Of the screenees eventually diagnosed with cancer, 248 were diagnosed at Kyoto Saiseikai Hospital.

As previously described, the PSAD was calculated to determine the necessity of prostate biopsy. The serum PSA level was 4.1–10.0 ng/mL in 86% of the first-time screenees. Of these screenees, the PSAD > 0.15 or DRE was positive in 496 (65%), of whom prostate needle biopsy was performed in 482 (98%). In the screenees who underwent prostate needle biopsy, cancer was detected in 24% (118/487) and 52% (65/124) of those in whom the PSA level was 4.1–10.0 ng/mL and 10.1 ng/mL or higher, respectively. Of the 269 screenees in whom biopsy was not indicated based on the PSAD in the initial secondary screening (Fig. 2), 147 underwent secondary screening again, and prostate cancer was detected in 23.

The serum PSA level was 4.1–10.0 ng/mL in 83% (1193/1439) of all who underwent secondary screening. Of these screenees, biopsy was indicated in 704 (59%) but not in 489 (41%), because no abnormality was noted during DRE, and the PSAD was 0.15 or less. Eventually, biopsy was performed in 665 (94%) of these 704 screenees, and prostate cancer was diagnosed in 151 (23%, 151/665). Of the screenees in whom the PSA level was 10.1 ng/mL or higher, prostate cancer was detected in 43% of those who underwent biopsy. Two screenees who showed a PSA level of 4.0 ng/mL or less underwent secondary screening with prostate needle biopsy, because their PSA level had been 4.1 ng/mL or higher in the past, but were thereafter excluded from prostate needle biopsy as no sign of malignancy was noted. Three screenees who showed a PSA level of 10.1 ng/mL or higher but were judged not to have an indication for biopsy had also undergone prostate needle biopsy in the past.

Table 3 shows the age distributions of all those who underwent secondary screening ($n = 1439$; 55–96 years; median, 71 years) and those in whom cancer was detected ($n = 248$; 55–92 years; median, 72 years) at Kyoto Saiseikai Hospital. In both groups, a peak was observed at 70–74 years, and 28% and 29% of the respective groups belonged to this age level. Table 4 shows the distribution of clinical stages in the screenees who were found to have cancer at Kyoto Saiseikai Hospital ($n = 248$). The disease in 193 (78%) of these patients was clinically localized prostate cancer (T1c-T2bN0M0). In particular, the percentage of patients with clinically T1cN0M0 cancer increased two-fold in the second five years compared with the first. The patients with locally advanced cancer (T3N0M0) numbered 35 (14%) and patients with metastatic cancer comprised 13 (5%) over the whole period.

Table 2 Frequency of patients with indications of biopsy, number of biopsies performed, and number of cancers detected according to the PSA level in those who underwent secondary screening

PSA(ng/ml)	No. of patients	Biopsy indicated	Biopsy not-indicated	Biopsied	Cancers
2-a First-time secondary screenees only					
4.1–10	765	496	269	482	118
10.1–	129	129	0	124	65
Total	894	625	269	606	183
2-b All secondary screenees					
≤4.0	2	0 (0%)	2 (100%)	0 (0%)	0 (0%)
4.1–10	1193	704 (59%)	489 (41%)	665 (56%)	151 (13%)
10.1–	243	240 (99%)	3 (1%)	223 (92%)	97 (43%)
Lack of PSA	1	0	1 (100%)	0	0
Total	1439	944 (66%)	495 (34%)	888 (62%)	248 (17%)

PSA, prostate-specific antigen.

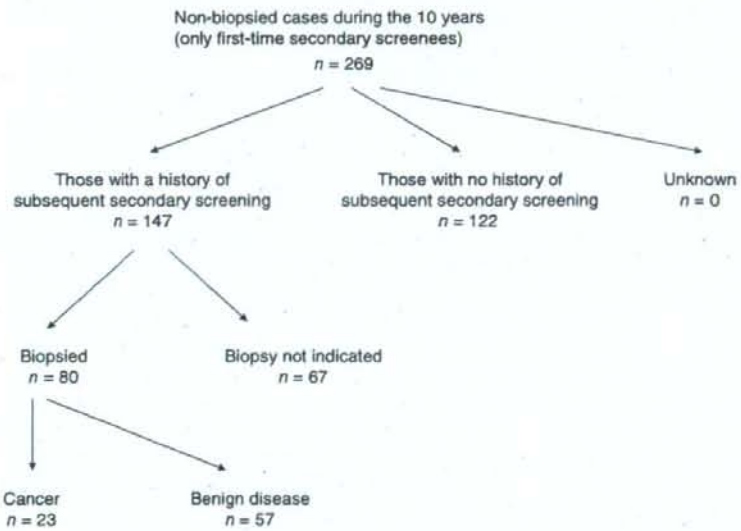

Fig. 2 Results of the follow-up of screenees in whom prostate needle biopsy was not conducted in secondary screening.

Although the ratio of clinically localized prostate cancer was 68% and the ratios of locally advanced cancer and metastatic cancer were both 27% from 1995 to 1999, the ratio of clinically localized prostate cancer between 2000 and 2004 increased by 15%, while that of locally advanced cancer and metastatic cancer within the same period decreased by 12%.

In this study, we calculated the total number of those who underwent primary screening during the 10-year period but could not calculate the number of those who were screened for the first time, because there was no system to discriminate first-time screenees and repeaters between 1995 and 1998. Therefore, the cancer detection rate in the true number of primary screenees cannot be calculated. In the Gunma Prefecture, in which prostate cancer screening has been performed annually for more than 10 years, the cancer detection rate was 1.13% (440/38 861).[8] To calculate the exposure rate of PSA screening in the Otokuni District, we tired to apply the detection rate of prostate cancer screening in the Gunma Prefecture. If the cancer detection rate in our study is assumed to have been similar to that in Gunma, the true number of primary screenees is estimated from the number of screenees in whom cancer was detected (267) to have been 23 628 (267/0.0113). Since the population of the Otokuni District aged 55 years and over was 22 705 in 2004, as mentioned above, all residents of the target population in this district are considered theoretically to have attended prostate cancer screening. This estimation may, of course, change with the method for the selection of candidates for secondary screening including the cut-off PSA levels for different age levels[9] and methods of prostate needle biopsy. Consequently, we tried to calculate the exposure rate of PSA screening using another method. In this study, the PSA level is considered to have been 4.1 ng/mL or above in 6.1% of all primary and secondary screenees during the 10-year period combined, and this value, calculated from the total number of screenees, is considered to reflect the true number of people with an abnormal PSA level in the Otokuni District. Therefore, of the 22 705 males aged 55 years and over in the Otokuni District, the PSA level is considered to be abnormal in

Table 3 Age distribution of those who underwent secondary screening ($n = 1439$) and those in whom cancer was detected ($n = 248$) at a core hospital

Age	Second screening	Cancer (detection rate)
55–59	32	10 (31%)
60–64	185	21 (11%)
65–69	378	52 (18%)
70–74	407	71 (17%)
75–79	243	45 (19%)
80–84	131	38 (29%)
85–89	47	8 (17%)
90–	16	3 (19%)
Total	1439	248
Mean ± SD	71.5 ± 7.0	72.5 ± 7.2
Median	71 years	72 years

SD, standard deviation.

Table 4 Distribution of clinical stages in the five-year periods of 1995–1999 and 2000–2004

Clinical stage	1995–1999	2000–2004	Total
T1cN0M0	23 (26%)	86 (54%)	109 (44%)
T2aN0M0	23 (26%)	31 (19%)	54 (22%)
T2bN0M0	14 (16%)	16 (10%)	30 (12%)
Sum of clinically localized cancer (T1c-2bN0M0)	60 (68%)	133 (83%)	193 (78%)
T3N0M0	17 (19%)	18 (11%)	35 (14%)
TxN1M0	0 (0%)	2 (1%)	2 (1%)
TxNxM1	7 (8%)	4 (3%)	11 (4%)
Unknown	4 (5%)	3 (2%)	7 (3%)
Total	88	160	248

1385 (22 705 × 0.06), since the number of those who were screened for the first time at the core hospital for secondary screening or other facilities was 903 men. In results, 65% (903/1385) of the target population in the Otokuni District is estimated to have undergone the PSA test.

Discussion

Basic health screenings are undertaken by a higher percentage of the population than other screening systems, and the percentage in the Otokuni District, Kyoto Prefecture (54.6%, 1999) is higher than the national average (44.8%, 2003). The Otokuni District was designated as a prostate cancer screening area, primarily because PSA examination was successfully incorporated in basic health screening, and because the system of referral from other hospitals and general practitioners to the core hospital (clinic-hospital cooperation) has been matured to a functional level.

Concerning reports on prostate cancer screening in Japan sponsored basically by local administrative organizations, Kuwahara *et al.* reported that 2212 were screened in Natori, Miyagi Prefecture during a 7-year period,[10] and Terai *et al.* reported that 1995 were screened in Okayama Prefecture during an 8-year period.[11] In the Otokuni District, the number of residents who attended primary screening increased, because about 80% of the screenees were screened individually as a result of the incorporation of the PSA test in basic health screening. Recently, PSA has also been examined as a part of basic health screening in other areas of Japan.[12]

In promoting screening for prostate cancer in a particular area, the percentage of the population in the area previously exposed to the PSA test (exposure rate) must be estimated to set the target age level of the screening. We tried to calculate the exposure rate of PSA screening using two methods. Despite the difference between the above two values, the exposure rate in the Otokuni District is considered to be high as a value of annual screening in local municipalities compared with 5.3% in the Gunma Prefecture,[8] and comparable to the value in the United States.[13]

To improve the detection rate of prostate cancer, the efficient selection of screenees for secondary screening including prostate needle biopsy is necessary. In the Otokuni District, people aged 55 years and over are screened. In Japan, the cancer detection rate in the population aged 50–54 years is 0.10%, which is lower than 0.25–2.55% in other age levels, but the evaluation of whether the screening age should be lowered to 50 years may become necessary in the future in consideration of the importance of early detection in younger patients.[14]

For the efficient selection of screenees for prostate needle biopsy, the use of the age-specific PSA reference,[9] PSA velocity,[15] and free/total PSA ratio[16] as well as PSAD, which we are using, has been reported. Our evaluation was negative regarding the usefulness of the age-specific PSA reference for prostate cancer.[17] However, Ito *et al.* reported that the age-specific PSA reference range cut-off value in this setting demonstrated a better diagnostic efficiency than the standard cut-off value of PSA and the age-specific PSA reference range determined by the 95% confidence interval.[9] Annual calculation of the PSA velocity in screenees with an initial PSA level of 1.0–4.0 ng/mL has been reported to have improved the diagnostic accuracy of prostate cancer.[15]

While various factors have been proposed by different institutions for the proper selection of candidates for prostate biopsy, no conclusion has been reached as to which is the optimal parameter for the evaluation of the indication for the procedure. On the basis of the evidence shown by the Watanabe Team,[5] we have evaluated the indication for biopsy according to the PSAD for 10 years. There has been no report on the use of the PSAD for mass screening, but, of the screenees undergoing secondary screening for the first time, prostate cancer was detected in 24% (118/487) and 52% (65/124) with PSA levels of 4.1–10.0 ng/mL and 10.1 ng/mL or higher, respectively. The cancer detection rate based on the PSA range was comparable to the average detection rate in Japan.

Of the 1436 screenees in whom the PAS level was 4.1 ng/mL or higher, biopsy was indicated in 944 (66%), and it could be circumvented in 492 (34%). Of the screenees who underwent secondary screening for the first time and were exempted from biopsy, because their PSA level was below the cut-off value, only 16% (23/147) were later diagnosed to have prostate cancer, and a considerable part of the screenees were repeatedly screened. An appropriate number of screenees should be selected for biopsy in consideration of the ability of the pathologists handling biopsies in the area, but this should not allow cancer to be overlooked. While the PSAD is useful for avoiding unnecessary biopsies, the fact that 45.3% (122/269) of the screenees did not undergo secondary screening thereafter suggests that the education of PSA-positive individuals to serially attend prostate cancer screening is necessary to maintain the reliability of the screening system.

Ito *et al.*[18] detected prostate cancer in 440 screenees by prostate cancer screening in the Gunma Prefecture between 1992 and 2001, and reported that the median age of patients was 69–71 years and that the percentage of patients with T1c/T2N0M0 disease was 56.3–76.9% during those 10 years. The age of patients and the clinical stage of the disease were very close to our results. The European Randomized Study of Screening for Prostate Cancer (ERSPC) also reported that the stage of the disease in 84.4% of the cancers detected in 1269 patients by screening was T1c/T2N0M0, and prostate cancer was detected in an early stage by screening.[19] In both the Otokuni District and the Gunma Prefecture,[18] where screening has been performed annually, prostate cancer tends to be detected at a progressively earlier stage. The American Urological Association sets a life expectancy of 10 years or longer as a criterion for the screenee selection for prostate cancer, and, of the randomized controlled trials reported in the past, the Quebec Study[20] set 80 years, and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening[21] set 74 years as the upper limit of screenees' age. Therefore, comparison of the age of patients at the time of detection of prostate cancer between our and the above studies is impossible.

Since the mean age of prostate cancer patients registered in Japan was 71.8 years at diagnosis,[22] no young age migration was suggested in the prostate cancer patients detected by screening in Gunma or Otokuni. For the future, comparison of the prostate cancer mortality rate between the whole of Japan and the Otokuni District is indispensable to examine whether the high PSA exposure and early detection rates by this screening system are causing lead time bias.

Conclusion

The results of prostate cancer screening in which the PSAD is used for secondary screening are presented. In Japan, the use of the basic health screening system leads to a wider recognition of primary prostate cancer screening and increases in the screening rate. In the Otokuni District, the PSA exposure rate was extremely high (65% with the application for the rate of screenees whose PSA level was 4.1 ng/mL or above), and whether this leads to a decrease in prostate cancer mortality must be evaluated. Comparative analysis of the PSAD with the age-specific PSA reference, free/total PSA ratio, and PSA velocity with regard to the appropriate setting of the interval and quality control of primary screening and detailed evaluation of the frequency of insignificant cancers using total prostatectomy specimens are necessary.

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