70 Gy. The identical radical radiotherapy was used in the experimental study arm with the addition of AK-2123.

In the study arm, patients received 0.6 g/sqm AK-2123 by intravenous administration 20—30 min before external beam radiotherapy, treating with AK-2123 on alternate days (e.g. Monday—Wednesday—Friday) during the entire course of external beam therapy.

Follow-up examinations were required at the end of radiotherapy, one month after radiotherapy, at regular intervals, every 4 months during the first two years, thereafter 6 monthly during the next 2 years and yearly thereafter.

Statistical analysis

Patients were randomised to either radical radiotherapy treatment (RT) or radical radiotherapy treatment with administration of AK-2123. Patients were stratified by centre.

Response rate and overall survival were chosen as endpoints for the study. Analysis of patient characteristics was performed using all randomised patients. For the further analysis, 7 patients were excluded since they never appeared for treatment and were lost to follow up. Thus, a total of 326 patients were analysed, on an intention to treat basis. Product limit estimates of survival distribution were calculated by the Kaplan—Meier method. The log-rank test was used to assess significant differences between survival curves and the χ^2 test was used to assess factors influencing tumour control between the treatment groups.

Results

The total number of patients available for analysis of acute toxicity after exclusion of the 7 patients who did not have treatment is 326. The median time of follow up is 50 months at analysis, the mean follow up for surviving patients is 32 months.

Tolerance of therapy

Acute toxicity. Local, gastro-intestinal toxicity did not differ significantly in the two treatment groups (utilising WHO criteria). There was no haematological toxicity following administration of AK-2123. There was a significant proportion of patients in the AK-2123 arm who experienced peripheral neuropathy. Seventeen patients developed grade 1 and three patients developed grade 2 peripheral neurotoxicity compared to none in the radiotherapy-only arm ($p < 0.0001$). In most cases these findings had normalised within 6 months. One patient has been recorded with mild, permanent peripheral neuropathy. A summary of acute toxicity is shown in Table 2.

Late toxicity. Patients on follow up for more than 2 months from randomisation were analysed for late toxicity to the bladder and rectum. There was no significant increase in the late toxicity in the AK-2123 treated patients. Bladder grade 1 toxicity was seen in 2 cases after radiotherapy alone and in 4 cases after AK-2123 treatment, in one case a grade 2 toxicity was recorded after AK-2123 treatment. Rectal late toxicity grade 2 was recorded in 4 patients after AK-2123 treatment compared to 3 after radiotherapy alone. One patient experienced grade 3 toxicity after radiotherapy alone.

Initial treatment response

The initial rate of complete response as determined at the end of radiotherapy or at the first follow up examination (within 4—6 weeks after completion of therapy) showed a statistical advantage for those patients treated with radiotherapy combined with AK-2123 compared to radiotherapy

Table 2
Acute toxicity (WHO criteria)

		Radiotherapy		AK-2123 and radiotherapy	
Upper GI	Grade 0	71/84	85%	60/86	70%
	Grade 1	8/84	8%	23/86	27%
	Grade 2	3/84	4%	3/86	3%
	Grade 3	2/84	2%	—	
Neurology	Grade 0	128/128	100%	112/132	85%
	Grade 1	—		17/132	13%
	Grade 2	—		3/132	2%
	Grade 3	—			—
Lower GI	Grade 0	103/142	73%	87/132	66%
	Grade 1	21/142	15%	25/132	19%
	Grade 2	15/142	13%	17/132	13%
	Grade 3	3/142	2%	3/132	2%
Bladder	Grade 0	113/141	80%	113/133	85%
	Grade 1	21/141	15%	12/133	9%
	Grade 2	7/141	5%	6/133	5%
	Grade 3	—		1/133	1%

alone (65% vs. 52%, $p = 0.01$, 99/153 vs. 86/167). This difference was also seen in subgroup analysis. In patients with stage IIIA disease (68% [17/25] vs. 60% [18/30]) and stage IIIB: 75% [91/130] vs. 54% [76/141]. Similarly for performance status 0 (84% [37/44] vs. 79% [37/47]) and for performance status 1 or 2 (70% [76/109] vs. 61% [73/120]), for patients being anaemic (Hb < 10 g/dl) 64% [37/58] vs. 51% [24/47] compared with those with a Hb of 11 g/dl or above: 65% [62/95] vs. 50% 61/121].

Distant metastases

A total of 24 patients have developed distant metastases. They were seen in both groups of patients. Sixteen patients in the RT group and 8 in the AK-2123 group have developed distant metastases with bone and lung being most frequent.

Local tumour control and actuarial survival

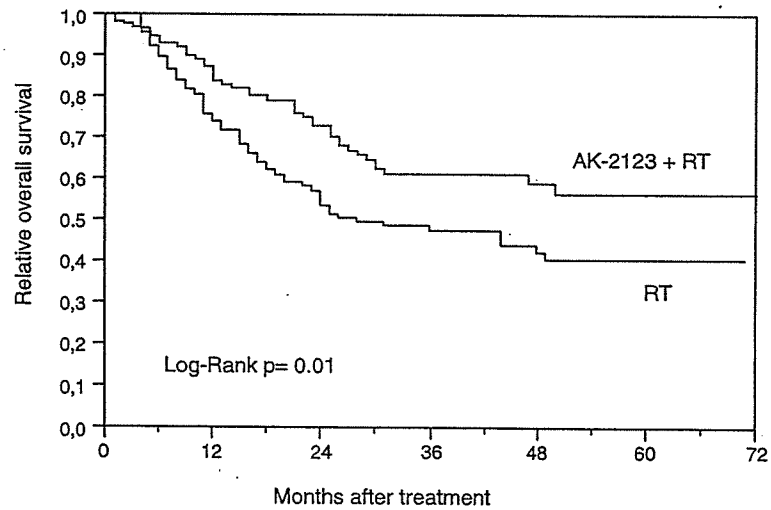
The rate of local tumour control was significantly higher in the group after radiotherapy and additional administration of AK-2123. Including patients who did not attend follow up examinations the rate of local tumour control was 61% (94/153) after AK-2123 and 46% (78/170) after radiotherapy alone ($p = 0.005$). The difference between AK-2123 and radiotherapy compared to radiotherapy alone was again seen when subgroups were analysed (stage, performance status and haemoglobin). The actuarial survival at 60 months was 57% (7/12) after RT+AK-2123, compared to 41% (5/11) after RT (Log Rank $p = 0.01$).

The overall rate of patients known to have died after combined treatment was 30% (47/155) compared to 44% (76/171) after radiotherapy alone ($p = 0.01$).

Figs. 1 and 2 depict actuarial survival and local regional control.

Discussion

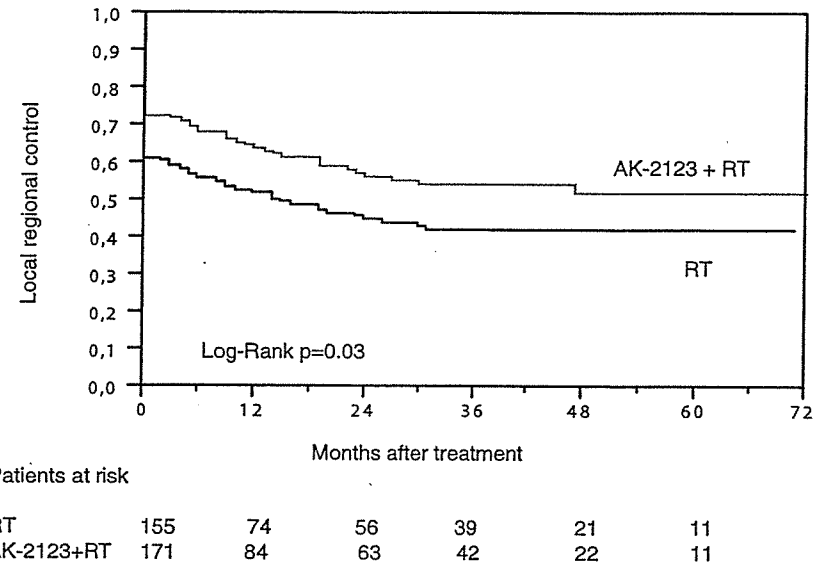
Results of radiotherapy in treatment of advanced uterine cervical cancer remain poor. Methods to increase the efficacy of radiotherapy have included combinations with chemotherapy and the use of radiosensitizers. Until recently, these combinations were not considered to be of general benefit for patients and did not have any major effect with regard to altering treatment standards. In 1999 three trials demonstrated an increase in local control and survival with regimens including cisplatin [14,15,20]. Cisplatin was believed to act as a radiosensitizer in these studies. In spite of side effects of combined therapy, many centres changed their treatment standards to combinations using cisplatin and radiotherapy in advanced cervical cancer, even though a Canadian study had found no improvement with additional cisplatin and the effect in stage III remained inconclusive [18]. More recent data suggest no significant benefit for chemo-radiotherapy with cisplatin compared to radiotherapy alone [2,19]. Morbidity is significantly increased when chemotherapeutic drugs are administered concurrently with radiotherapy, this has not only implications for the intensified care of patients but also rising costs for treatment of leucopenic septicaemia and hospitalisation of patients [22]. The present study shows promising results with a significant improvement similar to the reports on cisplatin and radiotherapy. Our results are comparable to meta-analyses in treatment of cervical cancer [8,21]. The advantage



Patients at risk

RT	155	101	73	45	24	12
AK2123 + RT	171	107	71	45	24	11

Fig. 1. Actuarial survival.



Patients at risk

RT	155	74	56	39	21	11
AK-2123+RT	171	84	63	42	22	11

Fig. 2. Local regional control.

of using AK-2123 is not only the improvement compared to radiotherapy alone, but also its relatively low toxicity, without any potentially life threatening haematological toxicity. Unlike nitroimidazole sensitizers, neurotoxicity was mild and generally transient. In clinical trials AK-2123 has been found to be well tolerated when administered with concomitant conventional fractionated radiotherapy, using doses of up to 1 g/sqm thrice weekly [11,13]. AK-2123 has also been used to sensitize accelerated fractionation radiotherapy in head and neck cancers. The results of this trial reported are significantly in favour of AK-2123 [12].

We found no increase in severe late toxicity after additional administration of AK-2123. The plasma half-life of $5\frac{1}{2}$ h, with most of the drug being eliminated within 24 h, means that it is useful for fractionated administration throughout a course of radiotherapy, without the fear of drug accumulation and increased toxicity.

This study is larger than most studies using radiosensitizers in treatment of cervical cancers. Previous studies using sensitizers have either shown no effect [4,5,9,16,17], adverse effect [6] or advantage [1] with regard to local tumour control.

We conclude that the addition of AK-2123 to radical radiotherapy significantly increases local tumour control from 46% to 61% ($p = 0.005$) and survival from 41% to 57% ($p = 0.008$) in advanced squamous cell cancer of the uterine cervix. AK-2123 did neither increase local toxicity nor was it attributed to haematological toxicity. A mild peripheral toxicity, usually completely reversible, was infrequently seen after AK-2123 administration.

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Received 18 September 2006; received in revised form 7 November 2006; accepted 14 November 2006; Available online 11 December 2006

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Int J Clin Oncol (2006) 11:253–255
DOI 10.1007/s10147-006-0576-3

EDITORIAL

Concurrent chemoradiation for cervical cancer: what should we do next?

Article on page 309

Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix

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Received: March 29, 2006

Several randomized trials have demonstrated the therapeutic advantage of concurrent chemoradiotherapy (CCRT) over radiation alone in the treatment of locoregionally advanced uterine cervical cancer.[1–4] Consequently, CCRT is now considered a standard treatment component for patients with uterine cervical cancer. In these trials, cisplatin was used alone or in combination with 5-fluorouracil (5-FU). Rose et al.[2] demonstrated similar survival results and less toxicity with weekly cisplatin compared with moderate-dose cisplatin and 5-FU in a Gynecologic Oncology Group (GOG) study (GOG-120). Based on those results, weekly cisplatin (40 mg/m^2) is now a standard regimen in the United States. However, it should be noted that the average patient age in these studies is younger than that seen in clinical practice in Japan. The Japanese Patterns of Care Study (JPCS) demonstrated that the median age of Japanese cervical cancer patients treated with definitive radiotherapy was 70 years.[5] In contrast, 80%–90% of patients entered in the GOG studies were below 60 years of age.[2–4] Therefore, an original prospective clinical study of CCRT for Japanese patients has been encouraged to assess the feasibility and toxicity of weekly cisplatin at 40 mg/m^2.

In this issue of the *International Journal of Clinical Oncology*, Watanabe et al.[6] report the results of a phase I study of CCRT with single-agent cisplatin in Japanese patients with cervical cancer. They designed two dose-escalation programs for weekly and monthly schedules. Dose-limiting toxicities (DLTs) were investigated separately for both definitive and postoperative settings. Their DLT criteria were designed somewhat similarly to those of recent GOG phase I studies. Treatment delay (i.e., radiotherapy and chemotherapy) of greater than 7 days due to toxicity was defined as a DLT. The investigators observed that the two patients in the definitive CCRT arm and two of the three in the postoperative CCRT arm experienced DLT at the dose level of 40 mg/m^2 (maximum tolerated dose; MTD). Therefore, they recommended a cisplatin dose of 30 mg/m^2 for the weekly schedule. Similarly, they concluded that 75 mg/m^2 should be the recommended dose for the monthly schedule. From these results, they concluded that weekly cisplatin at a dose of 40 mg/m^2 was not feasible for Japanese patients.

To my knowledge, the GOG has not officially performed a phase I/II study of CCRT with weekly cisplatin at a dose of 40 mg/m^2. Therefore, there are no feasibility data for this protocol evaluated by standard DLT criteria, as Watanabe et al.[6] stated in their report. Keys et al.,[3] in GOG-123, showed that 90% of patients were able to receive four or more courses of cisplatin. Similarly, Rose et al.[2] reported that, in GOG-120, four or more courses could be delivered in over 90% of patients and that nearly half of all patients received all the planned courses (six courses) of cisplatin. However, these studies[2,3] did not describe the details or the number of patients who required treatment modification and/or treatment delay, especially in regard to cisplatin administration. As mentioned above, Watanabe et al.[6] have now stated explicitly that more than a 7-day treatment delay constitutes a DLT. Can we not conclude that 8–14 days of delay in cisplatin administration is clinically acceptable in CCRT? Watanabe et al.[6] reported that all patients with DLT experienced granulocytopenia on the day of the planned fourth cycle of cisplatin. If further waiting had been allowed for these patients, the fourth cycle might have been safely given, and this phase I study could have reached a different conclusion. Ohno et al.[7] reported another Japanese phase I study, from the National Institute of Radiological Sciences in Japan. They concluded that weekly cisplatin at 40 mg/m^2 was feasible for Japanese patients. In the Ohno study, a longer treatment delay was allowed; namely, 2 weeks for radiotherapy and 3 weeks for chemotherapy. It should be noted that these authors reported that four of five patients who developed DLT were able to receive the full course of radiotherapy without interruption. In their report, Watanabe et al.[6] also showed that most patients were able to receive the full dose of radiation despite developing DLT.

Regrettably, in their current article, Watanabe et al. did not provide a detailed toxicity profile. Table 1 shows the toxicities that have been reported for CCRT using weekly cisplatin at 40 mg/m^2. The article by Ikushima et al.[8] reports retrospective toxicity data for Japanese patients with cervical cancer who were given concurrent weekly cisplatin and radiotherapy. These authors decided to determine cisplatin

Table 1. Acute toxicity (grade 3 or more) of CCRT using weekly cisplatin at 40 mg/m^2

Author (study)	Year	No. of patients	Toxicity (grade 3/4) %			
			Hematological	Leukopenia	Thrombocytopenia	Gastrointestinal
Rose[2] (GOG-120)	1999	176	–	21/2	2/0	8/4
Keys[3] (GOG-123)	1999	183	18/3	–	–	9/5
Pearcey[10]	2002	127	6/0	–	–	11/5
Serkies[9]	2004	112	–	4/2	0	4/2[a]
Ohno[7]	2005	6	–	83/0	0	16/0
Ikushima[8]	2006	11	91/9	–	–	9/0

[a] Nausea/vomiting

dose according to patient age, with 40 mg/m^2 the dose for younger patients (under 65 years) and 30 mg/m^2 for older patients (65 years or over). They observed that all 11 patients treated with 40 mg/m^2 cisplatin developed grade 3 or greater hematological toxicity. In contrast to these Japanese series, severe hematologic toxicities have been reported to be less frequent in studies conducted in North America and Europe.[2,3,9,10] In Poland, Serkies et al.[9] reported data, from their routine clinical practice, on patient compliance and an acute toxicity profile for CCRT including weekly 40 mg/m^2 cisplatin. Seventy-four percent of their patients with cervical cancer received at least four cycles of cisplatin. They showed that nearly 40% of patients who did not receive the five planned cycles had reasons other than toxicity, such as delayed administration of the first cycle of chemotherapy. They reported that only 5% of patients experienced grade 3 or 4 leukopenia.

On the basis of these findings, what should we do next in CCRT for cervical cancer? I have concluded that a new phase I study seeking an optimal weekly cisplatin dose would have little value. It is important to note that a survival advantage has been demonstrated with cisplatin at the very dose of 40 mg/m^2, but not at a compromised lower dose. On the other hand, it is true that Japanese patients have experienced severe hematological toxicity more frequently than patients in North America and Europe. However, life-threatening toxicity has been uncommon, even in Japanese patients; most importantly, radiotherapy has rarely been interrupted by toxicities. Thus, I believe we should conduct a proper phase II study of CCRT with weekly cisplatin at 40 mg/m^2 for Japanese patients, to determine its toxicity profile and survival outcome. In designing the trial, a treatment modification rule for cisplatin administration should be carefully planned. For this purpose, a detailed description of supportive treatment, such as the use of granulocyte-colony-stimulating factor (G-CSF) should be included in the protocol.

In addition to the scheduling of chemotherapy, the radiotherapy method is another important problem to be investigated in a future trial of CCRT for cervical cancer. There are several differences between the United States and Japan in the radiotherapy methods used. The most notable differences are in the dose rates of intracavitary brachytherapy (ICBT) and the total dose of radiotherapy. Although a National Cancer Institute of Canada (NCIC) study[10] employed not only low-dose-rate (LDR) but also high-dose-rate (HDR) and medium-dose-rate (MDR) ICBT, all randomized studies from the United States have only utilized LDR.[1–4] In contrast, almost all patients in Japan have been treated with HDR-ICBT.[5] Therefore, it should be investigated whether CCRT with HDR-ICBT leads to the same favorable outcome and acceptable toxicity as those demonstrated in earlier randomized studies utilizing LDR-ICBT. In addition, a large variance between the United States and Japan in the total radiotherapy dose has been identified.[11] This is another reason to conduct a prospective phase II study using weekly cisplatin with HDR-ICBT in Japan. Trials of several new chemotherapeutic regimens for CCRT are now underway. Baseline CCRT data with a "standard chemotherapeutic regimen" obtained with Japanese patients will be essential to make proper comparisons with investigational CCRT regimens in future.

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Journal of Digital Imaging

Microcatheter Tip Enhancement in Fluoroscopy: A Comparison of Techniques

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We compared three techniques for enhancement of microcatheter tips in fluoroscopic images: conventional subtraction technique (CST); averaged image subtraction technique (AIST), which we have developed; and double average filtering (DAF) technique, which uses nonlinear background estimates. A pulsed fluoroscopic image sequence was obtained as a microcatheter was passed through a carotid phantom that was on top of a head phantom. The carotid phantom was a silicone cylinder containing a simulated vessel with the shape and curvatures of the internal carotid artery. The three techniques were applied to the images of the sequence, then the catheter tip was manually identified in each image, and 100 x 100 pixel images, centered at the indicated microcatheter tip positions, were extracted for the evaluations. The signal-to-noise ratio (SNR) was calculated in each of the extracted images from which the mean value of the SNR and its standard deviation (SD) were calculated for each technique. The mean values and the standard deviations were 4.36 (SD 3.40) for CST, 6.34 (SD 3.62) for AIST, and 3.55 (SD 1.27) for DAF. AIST had a higher SNR compared to CST in almost all frames. Although DAF yielded the smallest mean SNR value, it yielded the best SNR in those frames in which the microcatheter tip did not move between frames. We conclude that AIST provides the best SNR for a moving microcatheter tip and that DAF is optimal for a temporarily stationary microcatheter tip.

KEY WORDS: Microcatheter tracking, enhancement technique, subtraction technique, signal-to-noise ratio, comparison of techniques, fluorography, endovascular intervention

INTRODUCTION

The number of endovascular interventions performed for patients with intracranial aneurysms is increasing. These interventions are less invasive than conventional surgery for intracranial aneurysms. In these endovascular interventions, coils, stents, and angioplasty balloons are transported via microcatheters. In such interventions, knowledge of the 3-dimensional (3D) position of the guide wire, the catheter tip, or the microcatheter tip relative to the vascular structures may facilitate the interventions, but determination of the 3D catheter position is difficult because the fluoroscopic image that is usually employed is 2-dimensional and noisy. Magnetic resonance imaging-based navigation systems have been investigated.[1–7] These systems can provide accurate 3D information during intervention, but they also require particular hardware; moreover, special

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Online publication 5 September 2006
doi: 10.1007/s10278-006-0855-6

care and devices are needed because of the magnetic field. Other investigators have proposed methods that provide 3D catheter positions by using devices which transmit electromagnetic signals to allow detection and tracking of a catheter tip in a body in conjunction with conventional x-ray angiography systems.[8,9] Image-based techniques[10] have been proposed for cardiac interventions, which align a catheter model with the catheter image in a single plane C-arm image using the projection Procrustes method.[11] Others have developed techniques to detect guide wires in fluorograms.[12–14]

We are developing an image-based system (the computer-assisted catheter guide system) to help with the navigation of catheters during an intervention for intracranial aneurysms.[15] Specifically, this system will provide image-based 3D catheter locations. However, for full automation and image fusion with this system, the catheter must be detected and tracked automatically and accurately in the images. To facilitate catheter detection, we have developed three catheter enhancement techniques. In this article, we compare these three catheter enhancement techniques in terms of the resulting signal-to-noise ratio (SNR). Evaluations were performed by using a fluoroscopic image sequence of a catheter as it was passed through a carotid phantom.

MATERIALS AND METHODS

A fluoroscopic image sequence of a catheter passing through a carotid phantom was obtained. The images were processed by using three different enhancement techniques: a conventional subtraction technique, a weighted sum of previous images, and a signal extraction technique involving local averages of local pixel values. The quality of the enhancement was evaluated by using the SNR of the resulting signal.

Fluorograms

A digital 1,024 × 1,024 × 12 bit fluoroscopic image sequence of a microcatheter passing through a carotid phantom was acquired by using the CAS-8000 V (Toshiba America Medical Systems, San Francisco, CA, USA) C-arm angiography system. The carotid phantom (Fig. 1a) consisted of a 3-mm-diameter polyethylene tube fixed in a silicone cylinder. The tube was constrained or molded to have the 3D shape and curvatures of a "typical" carotid (as determined by a neuroradiologist). The carotid phantom was positioned on a head phantom (Fig. 1b) to provide images similar to those that would be obtained during interventions, specifically to provide bony structured background in the fluorograms. The carotid phantom was set on the head phantom in a lateral position, and then those phantoms were set on the table of the angiography system. The carotid phantom was filled with a glycerin–water solution that provided smooth movement of the microcatheter. A 2.5 F (0.833 mm) Fastrack-18 Infusion microcatheter (Target, Fremont, CA, USA) was placed in the phantom and drawn back during fluoroscopic acquisition (Fig. 2). The pulsed fluorograms were acquired at 30 frames/second using 94 kVp and 50 mA. The source–surface distance was 100 cm and the magnification was 1.35. The 7-in. image intensifier mode was used (pixel size = 0.174 mm). Total acquisition time was 3.0 s. After acquisition, the 90 images were transferred to our analysis computer.

Techniques

During interventions, the catheter is guided to the site of intervention by observing the progress of the microcatheter tip under fluoroscopy. This microcatheter tip consists of a radiopaque marker with dimensions smaller than 1 mm. The fluorograms used for guidance usually include bone background and are generally noisy because of low dose. To detect and track a microcatheter tip in fluorograms, techniques are required which suppress the bone background and provide good SNR for the catheter tip. In this article, we report on three techniques to achieve these goals: the conventional subtraction technique, the averaged image subtraction technique using temporal averaging we developed, and a double average filtering technique using spatial averaging.

Conventional Subtraction Technique

In the conventional subtraction technique (CST) (one of the simplest techniques to detect object motion between frames), the previous frame is subtracted from the current frame. Microcatheters are darker in fluorograms than background. Thus, the CST is defined as,

$$D_n(x,y) = f_{n-1}(x,y) - f_n(x,y) \quad n = 2,3,4,\ldots \tag{1}$$

$$D_n(x,y) = \begin{cases} 0 & \text{when } D_n(x,y) < 0 \\ D_n(x,y) & \text{otherwise} \end{cases} \tag{2}$$

where $D_n(x, y)$ and $f_n(x, y)$ are respectively the difference image and the image at time point or frame number n. From equation (2), we see that this technique uses a nonlinear process, i.e., if the value of $D_n(x, y)$ is negative, it is set to 0. This nonlinear process should improve SNR by eliminating signals that result from subtraction of high-intensity structures, eg, the catheter tip appearing in the $(n - 1)$ image. Using this technique, stationary structures will be removed, and moving structures will appear as brighter regions.

Averaged Image Subtraction Technique

Fluorograms are usually noisy because of the low dose. In the conventional subtraction technique, the resultant image can be noisier then the original. To reduce increment of noise and

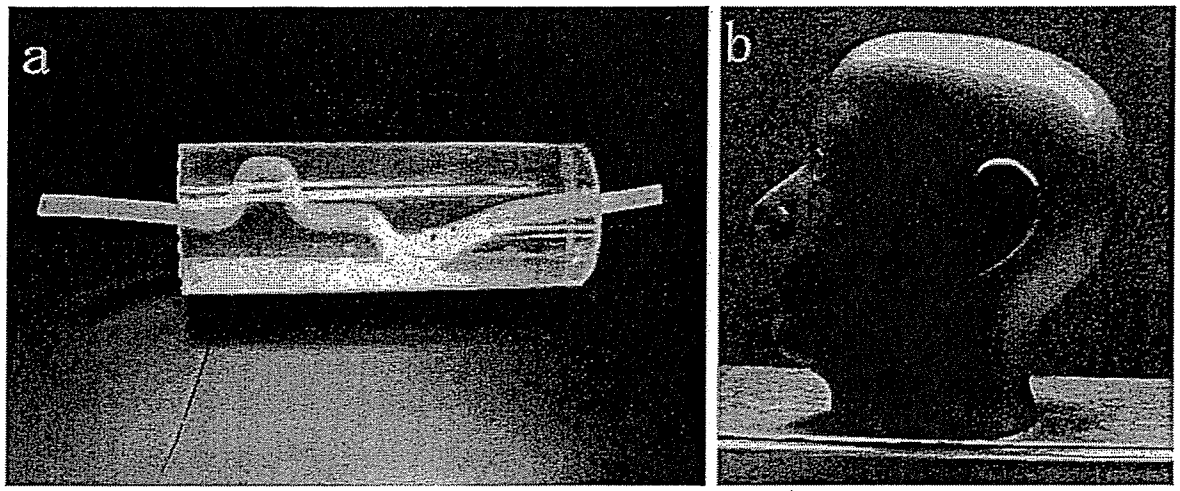

Fig 1. The carotid phantom and the head phantom. (a) A picture of the custom-made carotid phantom. The shape of the centerline of the tube fixed in silicon was based on carotid artery geometries observed by a neuroradiologist. (b) A picture of the head phantom that was used to provide structured background and scatter in the fluorograms.

to improve the SNR of the feature in the resultant image, we have developed a technique that uses an averaged image generated from the frames preceding the current frame and the current frame as a mask image. In this study, three preceding frames were used, thus, the averaged image is defined by the following equation.

$$A_n(x,y) = \frac{1}{4}\sum_{i=n-3}^{n} f_i(x,y), \quad n = 4,5,6,\ldots \tag{3}$$

where $A_n(x, y)$ is the averaged image, n is the frame number, and $f_i(x, y)$ is the original ith image. By using this averaged image as a mask image, the noise in the resultant images is less than that in the images generated using the CST. The equation for this technique in fluorograms in which catheters are darker than the background is thus as follows:

$$m_n(x,y) = A_n(x,y) - f_n(x,y) \qquad n = 4,5,6,\ldots \tag{4}$$

$$m_n(x,y) = \begin{cases} 0 & \text{when } m_n(x,y) < 0 \\ m_n(x,y) & \text{otherwise} \end{cases} \tag{5}$$

where $m_n(x, y)$is a resultant image, $A_n(x, y)$ is an averaged image generated by using equation (4), and $f_n(x, y)$ is the original ith image.

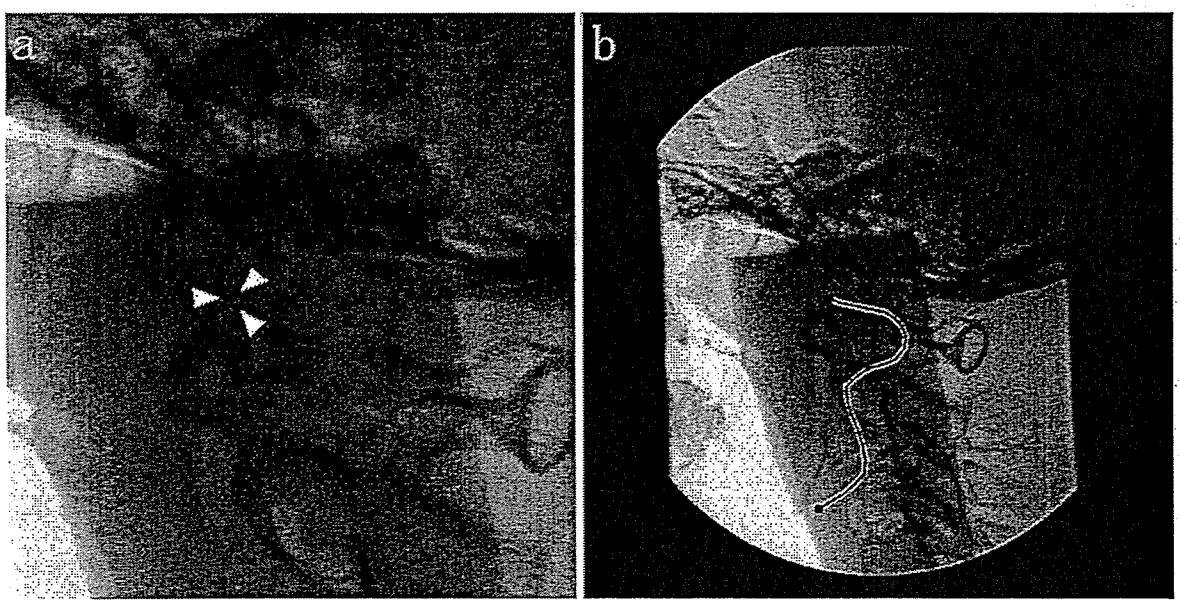

Fig 2. A microcatheter tip in a part of a magnified fluorogram and the path of the microcatheter. (a) White arrows point to the microcatheter tip. (b) The curve represents the path of the microcatheter tip in the sequence of fluorograms.

Note that this subtraction technique employs nonlinear processing similar to that used in the CST and that process could improve the SNR for this technique.

Double Average Filtering Technique

The double average filtering technique (DAF) was proposed as a preprocessing filtering for a vessel tracking technique for the coronary arteries in cine angiograms.[16] The authors indicated that the DAF did not amplify noise and did not generate artifacts that may result from conventional edge enhancement techniques. The double average filtering technique was defined as:

$$M_1(x,y) = \sum_{k=-w}^{w}\sum_{l=-w}^{w} f(x+k,y+l) \tag{6}$$

$$M_2(x,y) = \frac{\sum_{i=-w}^{w}\sum_{j=-w}^{w} f(x+i,y+j)W(x+i,y+j)}{\sum_{i=-w}^{w}\sum_{j=-w}^{w} W(x+i,y+j)} \tag{7}$$

where

$$W(x+i,y+j) = \begin{cases} 1 & \text{when } f(x+i,y+j) < M_1(x,y) \\ 0 & \text{otherwise} \end{cases} \tag{8}$$

$$\tilde{f}(x,y) = \begin{cases} f(x,y) - M_2(x,y) & \text{when } f(x,y) > M_2(x,y) \\ 0 & \text{otherwise} \end{cases} \tag{9}$$

where w is half-width of region of interest (ROI), $f(x, y)$ is the pixel value in the original image at coordinates (x, y), and $\tilde{f}(x,y)$ is the pixel value of final image after filtering by the DAF at coordinates (x, y). $M_1(x, y)$ is the average pixel value of all pixels in ROI, and $M_2(x, y)$ is the average pixel value of all pixels in ROI with pixel value less than $M_1(x, y)$.

Equation (9) is for the image with the signal intensity above the background. Although DAF is not only for such images, we inverted the pixel values in the fluorograms for DAF because the SNR for DAF was calculated by the same equation as for the others (see equation 10).

A size of ROI used in DAF is usually set to twice to triple the size of the feature. We investigated sizes of 5 × 5 up to 21 × 21; 15 × 15 yielded the best results. The size of the marker at the microcatheter tip in the fluorograms was about 5 × 5 pixels.

Measurement of Signal-to-Noise Ratio

To compare the three techniques described above, positions of the catheter tip in the fluorograms were first determined manually. Next, 100 × 100 pixel regions, centered at the indicated microcatheter tip positions were extracted from the fluorograms and processed by using the three techniques. We calculated SNR in each cropped image as:

$$SNR = \frac{\overline{S} - \overline{B}}{SD} \tag{10}$$

where, $\overline{S}$ is the mean pixel value in a 3 × 3 pixel region of 3 × 3 at the center of the extracted fluorograms (at the microcatheter

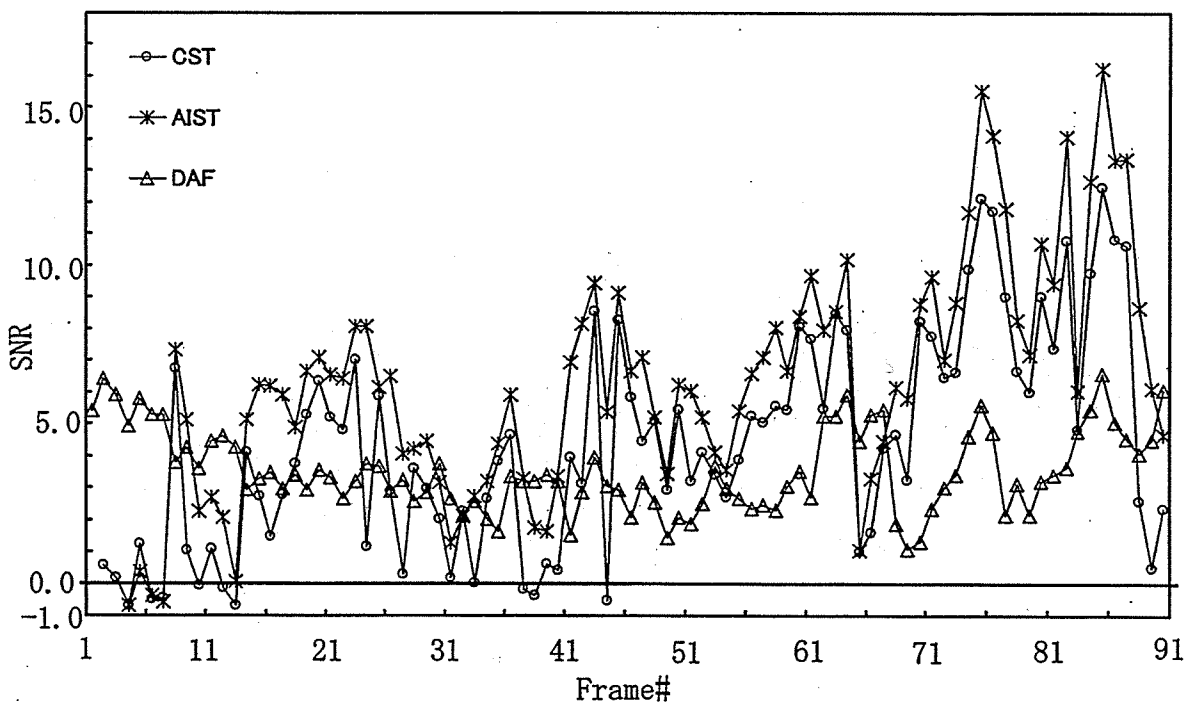

Fig 3. Variation of SNR for the three techniques. The AIST yields the best results, i.e., highest average SNR, whereas the DAF yields the lowest SD of the SNR values.

Table 1. Mean value and standard deviation of Signal-to-Noise Ratio in a sequence of fluoroscopy

Technique	CST	AIST	DAF
Mean value	4.36	6.34	3.55
Standard deviation	3.40	3.62	1.27

tip position), $\overline{B}$ is the mean value of the background, and SD is the standard deviation of background pixel values. A mean value of SNRs was also calculated from all the frames in the image sequence.

RESULTS

Variation in SNRs for each technique is shown in Figure 3, and mean values and SDs of SNRs for the three techniques are shown in Table 1. Based on mean values in Table 1, AIST has the highest overall SNR, and DAF has the lowest SNR but it also yielded the smallest SD. As shown in Figure 3, AIST and CST yielded negative SNR values in some frames, which occur when the catheter tip did not move between frames.

DISCUSSION

SNRs for AIST are similar to those for CST, but AIST showed higher SNRs than CST in almost all frames. It should be noted that AIST and CST are basically motion detectors and yield unreliable results (e.g., negative SNR values) when little or no motion occurs between frames (Fig. 4b and c). However, AIST resulted in fewer frames with negative SNR compared to CST. Thus, AIST appears to provide better enhancement than CST for microcatheter tip tracking in fluorograms.

The mean value of SNRs for DAF is less than those for AIST and CST. However, when the catheter tip does not move, DAF can provide an adequate SNR (Fig. 4d). Thus, AIST and DAF may complement each other in that AIST enhances the moving tip well and DAF enhances the stationary tip well.

When the microcatheter tip is on or near bony background, the tip is enhanced well with AIST and CST, whereas it is obscured with DAF because the local background averages (M_1 and M_2 in Double Average Filtering Technique) have lower pixel values. This is a limitation of DAF.

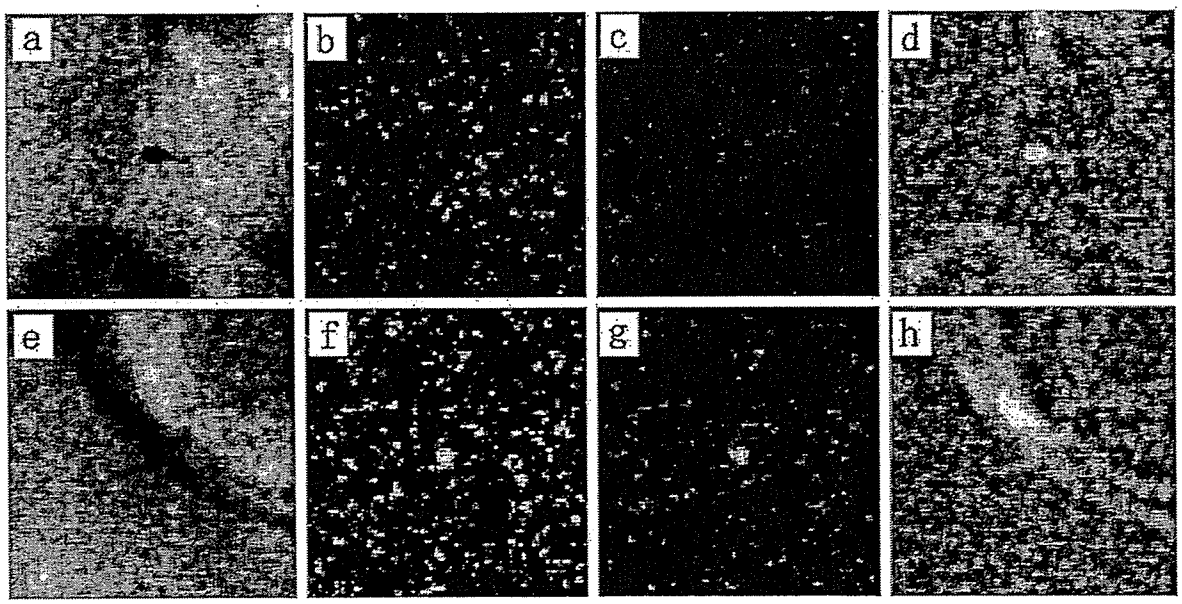

Fig 4. Examples of the original images and the images processed by the three techniques. (a) Original image of frame number seven in the sequential fluorograms. The images resulted from CST (b), AIST (c), and DAF (d). The image of the 7th frame is one of the images in which the catheter tip was not moved, so that the signals of the catheter tip in (b) and (c) have disappeared. (e) Original image of frame number 69 in the sequential fluorograms. The images resulted from CST (f), AIST (g), and DAF (h). The 69th frame is one of the images in which the catheter tip was on a bone edge. The DAF could not isolate the catheter tip signal.

In this study, fluorograms of the head phantom and the carotid phantom were obtained. We believe that addition of the carotid phantom did not affect our results, because each of the techniques estimates and subtracts out the local background. The carotid phantom introduced a slowly varying low-contrast background structure. Thus, the carotid phantom in the fluorograms probably only contributes in increasing the noise near the catheter tip.

CONCLUSIONS

Using SNR, we evaluated three techniques for tracking a microcatheter tip in fluorograms. From our results, we conclude that the averaged image subtraction technique (AIST) is the best of the three techniques for a moving microcatheter tip, and the double average filtering technique is useful for a nonmoving microcatheter tip.

ACKNOWLEDGMENTS

This research supported by a grant-in-aid for young scientists (B) (KAKENHI 15790656) of the Ministry of Education, Culture, Sports, Science, and Technology of Japan and NIH Grant numbers R01 HL52567, R01 EB 02916, R01EB002873, and R01NS43924.

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