

Fig. 1 臨床試験の基本要素

Table 2 臨床試験のデザイン

	目的	比較	評価指標・エンドポイント	対象
第I相	安全性・毒性の評価	過去のデータから導かれる安全性の許容水準と比較	最大耐容量DLT ¹ ・MDT ² の探索許容される毒性レベル	標準治療が奏効しなかった患者 (疾患要因は広くてもかまわないが、宿主要因は臓器機能が正常であること)
第II相	有効性の初期評価	過去のデータから導かれる有効性の水準と比較	有効性の短期的な代理エンドポイント 奏効率(割合)・CR率(割合)	特定の患者に限定 (疾患要因は特定で狭く、宿主要因はやや広く規定)
第III相	標準治療を決める	現在の標準的治療法と総合的な有用性を直接同時比較	有効性の真のエンドポイント 生存期間	第II相と同じ (疾患要因は特定で狭く、宿主要因は広い)
精度ベース試験	治療の精度を証明	なし	従来から行われている治療がある精度で有効・安全であるか前向きに症例登録して証明	標準治療が実施できる患者 (疾患要因・宿主要因は広く規定)
橋渡し試験	国内導入	国外の臨床試験データと比較	国外の臨床試験で認定された新標準治療の安全性と有効性の確認	

1 DLT (dose limiting toxicity) 2 MDT (maximum tolerable dose) 3 疾患要因: がん種・病期 4 宿主要因: 年齢・臓器機能

療を、医療の体制基盤が異なる日本に導入する際に実施される。

評価方法と判断規準は、試験の目的・相・対象・比較する治療法によって異なり、三つのシナリオに大別される (Fig. 2)。①「標準治療 対 強毒性の新治療」の場合は、少なくとも強毒性の不利益に見合うだけの有効性が認められなければ、臨床医は新治療を選ぶことはない。臨床的に意味のある差があるか統計学的に検証する。臨床的に意味ある差とは、「標準治療に対して新治療は、毒性が強いが有効性に大きな差があるので、臨床医は新治療を選ぶ」と言い換えられる。②「標準治療A 対 標準治療B、または同等毒性の

新治療」の場合は、両治療の毒性が同等であることが試験を通じて再確認されれば、わずかな有効性の差であったとしても優れた治療法が標準治療になる。③「標準治療 対 低毒性の新治療」の場合は、毒性が低いことが試験を通じて再確認され、新治療の有効性が許容下限以下にならなければ、低毒性の新治療が標準治療になる。

がん治療の多くは集学的治療であり、総合的に治療法を評価する必要がある。こうしたmulti-regimenの臨床試験では、検討する治療のパラメータにそって複数のアームを設定し、多段階登録を行い、適切に割付を行わなくてはならない。ランダム割付には、単純ラン

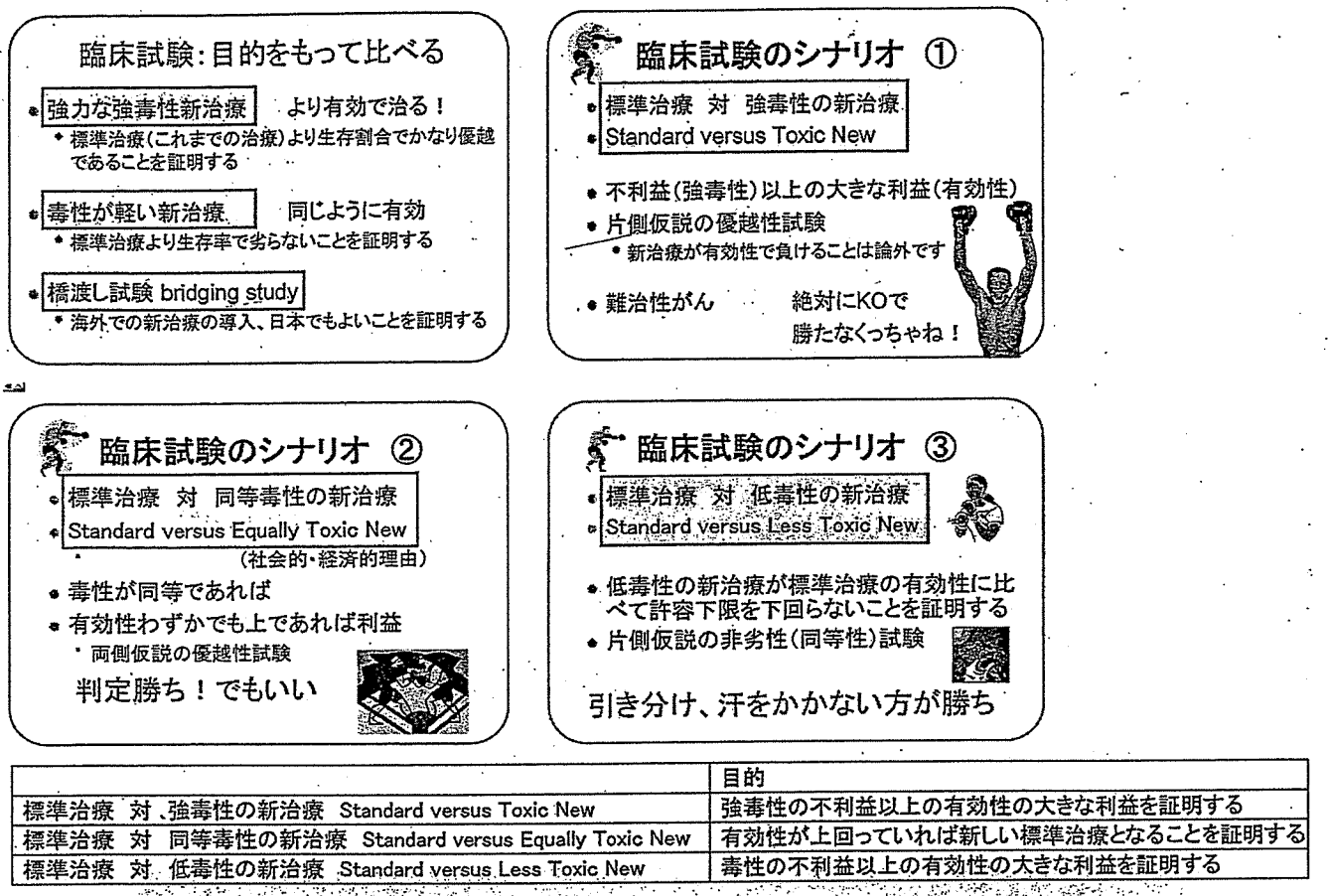


Fig. 2 臨床試験における判断規準: シナリオ

ダム割付・静的ランダム割付・動的ランダム割付があり、データセンターにて実施する。

6. 臨床試験のプロセス

臨床試験の企画プロセスは、コンセプトの立案・エンドポイントの決定・対象の決定・新治療と標準治療の明確化・評価方法の検討などの段階に分けられる。各段階で整合性を保たないと、矛盾点が生じるので、臨床試験の企画にあたっては、計画書を繰り返し読み合わせ、複数で検証する。企画検討委員会およびデータセンターで、内容を検証することが重要である。特に生物統計家による症例数の算定やデータサンプリングの検討は重要である。とかく生存割合など数値が一人歩きしやすいが、数値の意味する内容を正確に理解することが科学的判断には必要である (Fig. 3)。

臨床試験を開始する際には、多施設研究グループの臨床試験審査委員会での承認を経て、各参加施設の institutional review board (IRB) の承認を必要とする。実施中に計画書・プロトコルの内容を、追加・変更しなくてはならないことがある。患者の危険や負担を増大させたり、エンドポイントに関連する重大な改正 (amendment) の場合は、効果安全性評価委員会での審

査・承認を経て、各参加施設のIRBの再承認を必要とする。患者の不利益や負担がなくエンドポイントにかかわらない改訂 (revision) の場合や、解釈のばらつきを減らしたり注意を喚起する覚書 (memorandum) の場合は、効果安全性評価委員会へ報告し審査を受ける必要がある。

7. 放射線治療の品質保証と品質管理

臨床試験が正しい結果を得るには、治療がプロトコルを遵守して実施されなくてはならない。品質保証管理委員会にて、放射線治療の技術的かつ臨床的な品質保証作業を行う必要がある (Fig. 4)。また、処方線量が正しいか、照射野形状が正確であるか、など放射線機器が高い精度で保持されていることを示さなければならない。難しいプロトコルでは、治療開始時と治療中も放射線治療が安全かつ遵守されているかを支援していく活動が必要である。

8. まとめ

すべてのがんや治療法について臨床試験を行うことは不可能であり、稀な疾患や特殊な治療法の検討においては、必ずしも臨床試験が適した科学的研究方法で

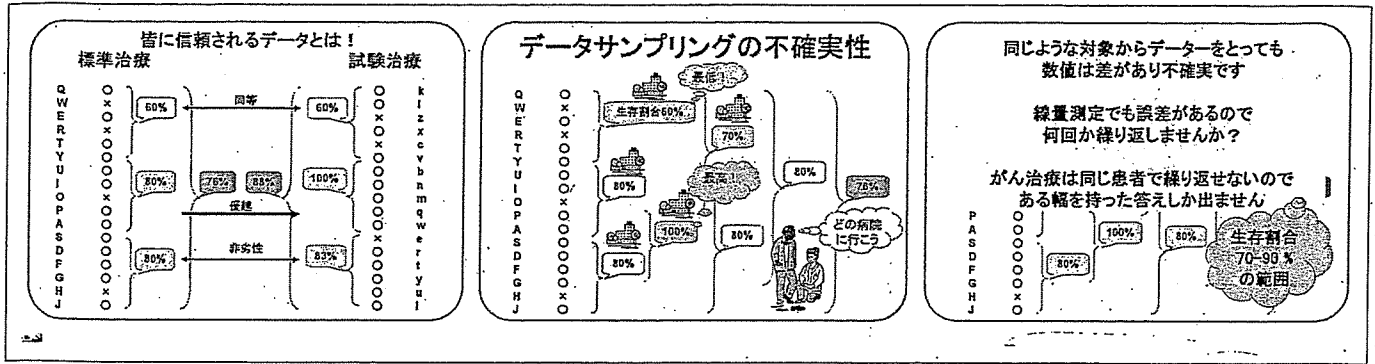


Fig. 3 データサンプリングの不確実性：生物統計家の役割

放射線治療の品質保証

- 治療部位の単純X線写真
- 病巣部を的確に示す診断画像
- X線シミュレーション写真
- リニアックグラム
- 放射線治療記録 (照射方向、X線エネルギー、処方線量、照射野サイズなど)

JAROG 0201

- QA-1) 放射線治療実施日
- QA-2) 1回線量
- QA-3) 総線量
- QA-4) 総治療期間
- QA-5) 放射線治療実施評価
- QA-6) エネルギー
- QA-7) GTVと線束との位置的關係
- QA-8) 標的基準点
- QA-9) 位置決め写真と照準写真(リニアックグラフィー)との照合

登録番号「@」
病巣部を的確に示す診断画像(キーマージ)

登録番号「@」
シミュレーション写真とリニアック・グラフィー

シミュレーション写真

リニアックグラフィー

Fig. 4 放射線治療の品質保証の例 JAROG 0201

はない。患者の視点に立って「真の利益」を検討する姿勢を忘れてはならない。しかし未来の多くの患者にとって、臨床試験は有益な科学的根拠をもたらす。祖父の時代の臨床試験結果が父母のがん治療に役立ち、

父母の時代の臨床試験結果が子供のがん治療に役立つように、世代を超えて進歩するための努力を惜しむべきではない。

参考文献

- 1) 厚生労働省がん研究助成金による研究報告集. 平成17年度 国立がんセンター, 東京, (2005).
- 2) Clinical trials in Oncology: Interdisciplinary statistics. 2nd Ed. (Ed) Green S, Benedetti J, Crowley J. Chapman & Hall/CRC, New York, (2002).
- 3) 福田治彦, 新美三由紀, 石塚直樹 訳: 米国SWOGに学ぶがん臨床試験を实践—臨床医と統計家の協調をめざして—. 医学書院, 東京, (2004).
- 4) EORTC Quality Control Group, Therasse P. (eds): A practical guide to EORTC studies. EORTC data center, Brussels, (1996).
- 5) 下山正徳: 質の高いがん臨床試験を実施する共同研究グループ機構の設立とその成果. 癌の臨床, 52(4), 301-359, (2006).
- 6) 石倉 聡, 石塚直樹, 福田治彦: 集学的治療の臨床試験デザイン. 臨床放射線, 48(12), 1499-1505, (2003).
- 7) <http://www.eortc.be>
- 8) <http://www.jcog.jp>
- 9) <http://www.rtog.org>

Phase III randomised trial

AK-2123 (Sanazol) as a radiation sensitizer in the treatment of stage III cervical cancer: Results of an IAEA multicentre randomised trial[☆]

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Abstract

Purpose: AK-2123, a nitrotriazole hypoxic cell sensitizer, has reportedly improved results in head and neck cancers, uterine cervical cancers and other solid tumours when added to radical radiotherapy. A prospectively randomised trial was initiated by the International Atomic Energy Agency (IAEA) evaluating AK-2123 and radiotherapy in treatment of uterine cervical cancer stage III and IV.

Patients and methods: A total of 462 patients were randomised from 8 centres. Patients from four centres were excluded due to lack of accrual, closing of the centre and insufficient documentation and reporting. The final study population consisted of 333 patients who were randomised between May 1995 and December 1998. Patients were randomised to either standard radical treatment (radiation therapy alone, RT) or standard radical radiotherapy and additional administration of AK-2123 (RT+AK-2123). The total dose of 45–50.8 Gy was delivered by 20–28 fractions in an overall time of 4–5½ weeks, with further dose escalation by brachytherapy or external beam. In the study arm, patients received 0.6 g/sqm AK-2123 by intravenous administration before external beam radiotherapy, treating with AK-2123 on alternate days (e.g. Monday–Wednesday–Friday) during the entire course of external beam therapy. Following exclusion of 7 patients who did not undergo treatment, a total of 326 patients remained for evaluation.

Results: The rate of local tumour control was significantly higher in the group after radiotherapy and additional administration of AK-2123. Local tumour control was 61% (95/155) after AK-2123 and 46% (79/171) after radiotherapy alone ($p = 0.006$). The actuarial survival at 60 months was 57% after RT+AK-2123, compared to 41% after RT (Log Rank $p = 0.01$). AK-2123 did neither increase gastro-intestinal toxicity nor was it attributed to any haematological toxicity. A mild peripheral toxicity (Grade 1: 13% and Grade 2: 2%) usually completely reversible was infrequently seen after AK-2123 administration.

Conclusion: We conclude that the addition of AK-2123 to radical radiotherapy significantly increases local tumour control and survival in advanced squamous cell cancer of the uterine cervix without the addition of any major toxicity. © 2006 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 82 (2007) 24–29.

Keywords: Radiotherapy; Hypoxic radiosensitizer; Cervical cancer

It is estimated that 470,000 cases of cancer of the uterine cervix were diagnosed in 2000. Early disease can be curatively treated either by surgery or irradiation but patients with locally advanced cervical cancer have a poor prognosis mainly due to failure to control the local disease with radiotherapy even though technique and methods of

treatment have improved over the last decade. In spite of the various efforts to enhance the efficacy of irradiation, local failure is still the main problem in these cases. One of the reasons of failure of radiation to achieve a better survival is the presence of a less radiosensitive hypoxic cell population [10]. Hyperbaric oxygen trials and blood transfusion studies have suggested that hypoxia is a major problem for tumour control in carcinoma of the cervix [3,24]. However, clinical trials to overcome the radioresistance with radiosensitizers have generally not shown a significant

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clinical benefit. The reason for this may be attributed to limitations of the sensitizer dose because of the neurotoxicity of the drug. Experimental data and preliminary clinical studies in the literature demonstrated that, a nitrotriazole derivative, AK-2123, is a hypoxic cell sensitizer with lower neurotoxicity than most nitroimidazoles [23]. Early studies testing AK-2123 as a radiosensitizer with irradiation in various tumours showed encouraging results [7,12].

A phase III randomised trial was designed in order to evaluate the sensitizing effect of the drug.

This multicentric randomised study was conducted under the auspices of IAEA and analysed complete data in July 2001 with participating centres from India, Sri Lanka, Pakistan and Turkey.

Patients and methods

Initially, a total of 462 patients were randomised from 8 centres. Four of the centres had to be excluded due to lack of randomisation (1), insufficient reporting and documentation (2) and closure of the centre (1). After further exclusion of 7 patients who did not start treatment 326 patients remained and were analysed. These patients were randomised between May 1995 and December 1998. Patients were randomised to either standard radical treatment (radiation therapy alone, RT) or standard radical radiotherapy and additional administration of AK-2123 (RT+AK-2123), a hypoxic cell radiation sensitizer. All patients were diagnosed with stage IIIA or IIIB squamous cell carcinoma of the uterine cervix. Inclusion criteria were patients up to 75 years at diagnosis, absence of distant metastases and no prior therapy for cancer (except skin cancer). The mean (=median) age of the patients at time of randomisation was 52 years. Prior to therapy all patients were informed about the randomisation and had given written informed consent to participate in the study. All centres participating in the trial did this after approval of their local Ethical Committee, respectively. Patients were stratified for centre of therapy. The characteristics of the patients in the two randomisation groups are seen in Table 1.

The distribution of the patients prior to therapy regarding stage, age, presence of hydronephrosis or bilateral disease and their haemoglobin level and performance status shows an equal distribution in the two groups.

Pharmacokinetics

AK-2123 (*N*-(2-methoxyethyl)-3-(3'-nitro-1'-triazolyl)acetamide) is a water soluble compound. It has an octanol to water coefficient of 0.15, which ensures decreased distribution of the drug in neural tissues including brain. The drug can be administered orally or parenterally. The drug is well absorbed following oral administration but takes time to achieve peak plasma level [11]. However, intravenous administration of the drug results in an almost instantaneous peak plasma level [11]. The pharmacokinetics of AK-2123 follows a two compartment model. The elimination of the drug from plasma follows a biexponential decay with

Table 1
Patient characteristics

	Radiotherapy	AK-2123 and radiotherapy
Total number (randomised)	173	160
Stage IIIA	30 (17%)	26 (16%)
Stage IIIB	143 (83%)	134 (84%)
Performance status		
0	51 (29%)	47 (29%)
1	121 (70%)	109 (68%)
2	1	4
Age (mean)	32–79 years (52)	27–73 years (51)
Hb (g/dl)	11.6 (5.2–19.7)	11.4 (4.5–15.3)
Hydronephrosis	9 (5%)	10 (7%)
Bilat. pelvic wall inf.	86 (50%)	80 (51%)
Total number treated	171	155
External beam dose (mean)	53 Gy	54 Gy
Patients receiving brachy-therapy	107	90
Dose to point A (mean)	68 Gy	65 Gy
Dose to point B (mean)	59 Gy	58 Gy

an elimination half-time of 5.18 h. Thus most of the drug is eliminated in 24 h and, cumulative toxicity of the drug is negligible. It is predominantly excreted in urine in unchanged form. Few 3-aminoderivatives have been isolated as metabolites of AK-2123 in urine.

Treatment

External radiation treatment was performed with Co-60 machines or by linear accelerators. Dose prescription was performed according to ICRU 38. The treatment volume comprised the primary tumour and pelvic lymph nodes. The upper field border was at L4/L5 or L5/S1, the lower border was at the obturator foramen, or at least one cm beyond palpable disease. The lateral borders were outside of the bony pelvis by at least 1–2 cm. Treatment was given by parallel opposed fields or a four-field arrangement (''box technique''). In the case of four-field technique, the upper and lower borders were identical as above, the ventral field border was the symphysis and the dorsal border parallels the anterior part of the S2/S3 region. The fraction sizes ranged between 1.8 and 2.25 Gy as measured in the mid-plane. The total dose of 45–50.8 Gy was delivered by 20–28 fractions in an overall time of 4–5½ weeks. This variety of doses and fractions is due to the individual participant's standard therapy and was maintained throughout the study and was the same in the two randomisation groups. Brachytherapy was performed either by HDR or LDR (Sources: Ir, Co, Cs) aiming to increase the dose in point A to at least 70.0 Gy by application of 1–3 fractions. If brachytherapy was not performed, the dose of external beam should be increased to ensure that the total dose in point A was at least

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

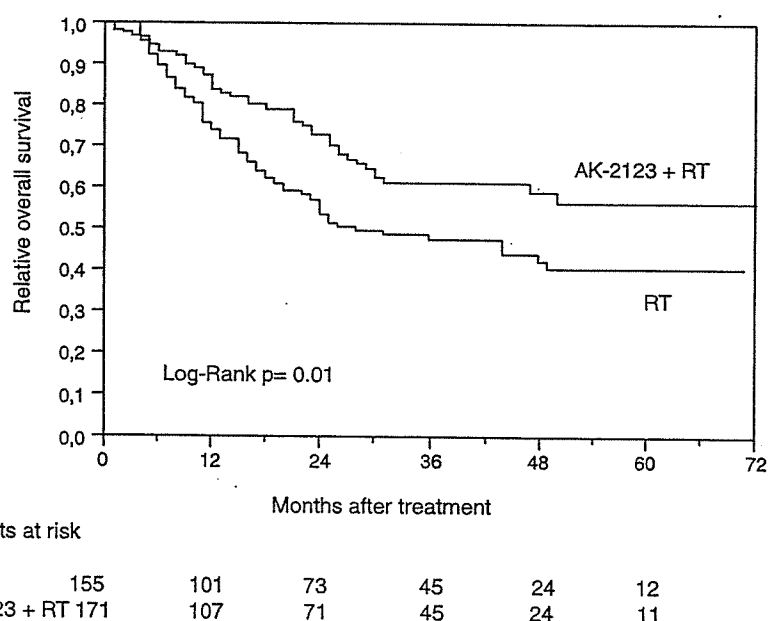


Fig. 1. Actuarial survival.

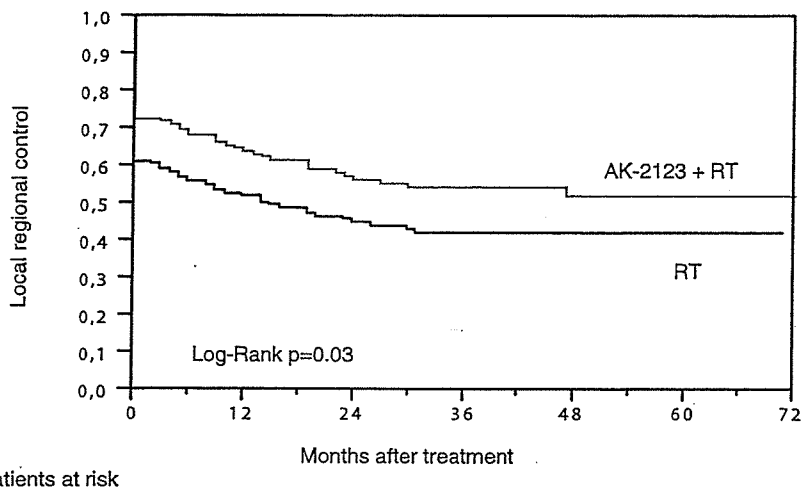


Fig. 2. Local regional control.

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 5½ 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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References

- [1] Balmukhanov SB, Beisebaev AA, Aitkolovo ZI, et al. Intratumoral and parametrial infusion of metronidazole in the radiotherapy of uterine cervix cancer: preliminary report. *Int J Radiat Oncol Biol Phys* 1989;16:1061–3.
- [2] Borowsky ME, Elliott KS, Pezzullo JC, et al. A retrospective review of 15 years of radical radiotherapy with or without concurrent cisplatin and/or 5-fluorouracil for the treatment of locally advanced cervical cancer. *Bull Cancer* 2005;92:19–24.
- [3] Bush RS. The significance of anemia in clinical radiation therapy. *Int J Radiat Oncol Biol Phys* 1986;12:2047–50.
- [4] Chan P, Milosevic M, Fyles A, et al. A phase III randomized study of misonidazole plus radiation vs. radiation alone for cervix cancer. *Radiother Oncol* 2004;70:295–9.
- [5] Dische S, Adams GE, Ash DV, et al. The Medical Research Council trial of misonidazole in carcinoma of the uterix. *Br J Radiol* 1984;57:491–9.
- [6] Dische S, Machin D, Chassagne D. A trial of Ro 03-8799 (pimonidazole) in carcinoma of the uterine cervix: an interim report from the Medical Research Council Working Party on advanced carcinoma of the cervix. *Radiother Oncol* 1993;26:93–103.
- [7] Gacia-Angulo AH, Kagiya VT. Intratumoral and parametrial infusion of a 3-nitrotriazole (AK-2123) in the radiotherapy of the uterine cervix cancer: stage II-III-preliminary positive result. *Int J Radiat Oncol Biol Phys* 1992;22:589–91.
- [8] Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;358:781–6.
- [9] Grigsby PW, Winter K, Wasserman TH, et al. Irradiation with or without misonidazole for patients with stages IIIB and IVA carcinoma of the cervix: final results from of RTOG 80-05. *Int J Radiat Oncol Biol Phys* 1999;44:513–7.
- [10] Höckel M, Schlenger K, Aral B, et al. Association between tumour hypoxia and malignant progression in advanced cancer of the uterine cervix. *Cancer Res* 1996;56:4509–15.
- [11] Huan LC, Hua BY. Clinical pharmacokinetic study and sensitive effect of AK-2123. *Int J Radiat Oncol Biol Phys* 1994;29:607–10.

- [12] Huilgol NG, Chatterjee N, Mehta AR. An overview of the initial experience with AK-2123 as a hypoxic cell sensitizer with radiation in the treatment of advanced head and neck cancers. *Int J Radiat Oncol Biol Phys* 1996;34:1121–4.
- [13] Kagiya VT. AK-2123 Chemical modifier of cancer treatment, part I. Int. Coordinated Research Program. *Jpn Radiosensitization Res Ass Kyoto Japan* 1993.
- [14] Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *NEJM* 1999;340:1154–61.
- [15] Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *NEJM* 1999;340:1137–43.
- [16] Okkan S, Atkovar G, Sahinler I, et al. A randomised study of ornidazole as a radiosensitiser in carcinoma of the cervix: long-term results. *Br J Cancer* 1996;74:5282–6.
- [17] Overgaard J, Bentzen SM, Kolstad P, et al. Misonidazole combined with radiotherapy in the treatment of carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1989;16:1069–72.
- [18] Pearcey RG, Brudage P, Drovinn J, et al. A clinical trial comparing concurrent cisplatin and radiotherapy versus radiotherapy alone for locally advanced squamous cell carcinoma of the cervix. Carried out by the National Cancer Institute of Canada Clinical Trials Group. *Proc Am Soc Clin Oncol* 2000;19:378.
- [19] Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002;20:966–72.
- [20] Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *NEJM* 1999;340:1144–52.
- [21] Rose PG. Chemoradiotherapy for cervical cancer. *Eur J Cancer* 2002;38:270–8.
- [22] Serkies K, Jassem J. Concurrent weekly cisplatin and radiotherapy in routine management of cervical cancer: a report on patient compliance and acute toxicity. *Int J Radiat Oncol Biol Phys* 2004;60:814–21.
- [23] Shibamoto Y, Sakano K, Kimura R, et al. Radiosensitization in vitro and in vivo by 3-nitrotriazoles. *Int J Radiat Oncol Biol Phys* 1986;12:1063–6.
- [24] Watson ER, Halnan KE, Dische S, et al. Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. *Br J Radiol* 1978;51:879–87.

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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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/m²) 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/m².

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/m² (maximum tolerated dose; MTD). Therefore, they recommended a cisplatin dose of 30 mg/m² for the weekly schedule. Similarly, they concluded that 75 mg/m² should be the recommended dose for the monthly schedule. From these results, they concluded that weekly cisplatin at a dose of 40 mg/m² 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/m². 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/m² 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/m². 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 40mg/m²

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

^aNausea/vomiting

dose according to patient age, with 40mg/m² the dose for younger patients (under 65 years) and 30mg/m² for older patients (65 years or over). They observed that all 11 patients treated with 40mg/m² 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 40mg/m² 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 40mg/m², 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 40mg/m² 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) study¹⁰ 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.

References

- Morris M, Eifel PJ, Lu J, et al. (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 340:1137-1143
- Rose PG, Bundy BN, Watkins EB, et al. (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 340:1144-1153
- Keys HM, Bundy BN, Stehman FB, et al. (1999) Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 340:1154-1161
- Whitney CW, Sause W, Bundy BN, et al. (1999) Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol* 17:1339-1348
- Toita T, Nakamura K, Uno T, et al. (2005) Radiotherapy for uterine cervical cancer: results of the 1995-1997 Patterns of Care Process survey in Japan. *Jpn J Clin Oncol* 35:139-148
- Watanabe Y, Nakai H, Shimaoka M, et al. (2006) Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase 1 study in Japanese patients with cancer of the uterine cervix. *Int J Clin Oncol* 11:309-313
- Ohno T, Kato S, Tsujii H (2005) Phase I study of weekly cisplatin plus radiotherapy for locally advanced cervical cancer (in Japanese). *Jpn J Gynecol Oncol* 23:564-571

8. Ikushima H, Osaki K, Furutani S, et al. (2006) Chemoradiation therapy for cervical cancer: toxicity of concurrent weekly cisplatin. *Radiat Med* 24:115-121
9. Serkies K, Jassem J (2004) Concurrent weekly cisplatin and radiotherapy in routine management of cervical cancer: a report on patient compliance and acute toxicity. *Int J Radiat Oncol Biol Phys* 60:814-821
10. Pearcey R, Brundage M, Drouin P, et al. (2002) Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 20:966-972
11. Toita T, Kakinohana Y, Ogawa K, et al. (2003) Combination external beam radiotherapy and high-dose-rate intracavitary

brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 56:1344-1353

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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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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 techniques¹⁰ 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 $1,024 \times 1,024 \times 12$ 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 radio-opaque 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,

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

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

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 than the original. To reduce increment of noise and

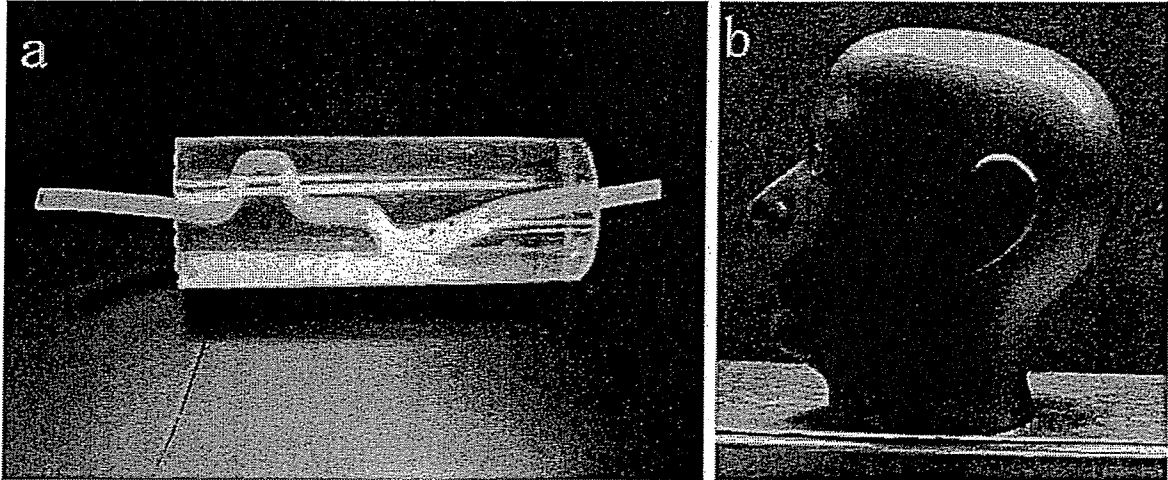


Fig 1. The carotid phantom and the head phantom. (a) A picture of the custom-made carotid phantom. The shape of the centerline of the tube fixed in silicon was based on carotid artery geometries observed by a neuroradiologist. (b) A picture of the head phantom that was used to provide structured background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

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

where $A_n(x, y)$ is the averaged image, n is the frame number, and $f_i(x, y)$ is the original i th 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:

$$m_n(x, y) = A_n(x, y) - f_n(x, y) \quad n = 4, 5, 6, \dots \quad (4)$$

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

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 i th image.

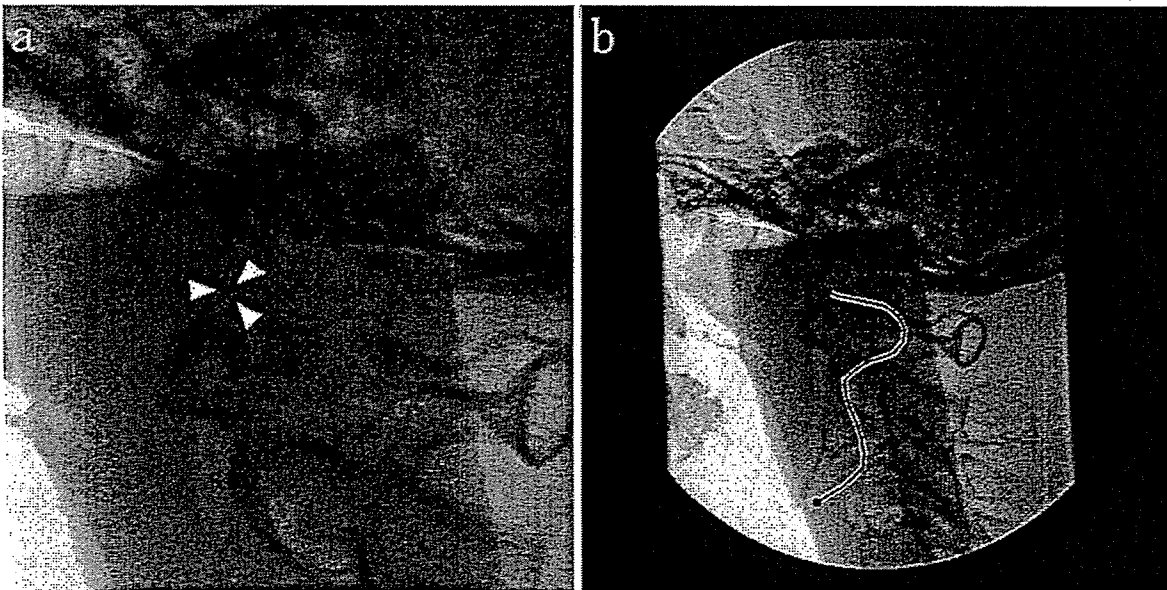


Fig 2. A microcatheter tip in a part of a magnified fluorogram and the path of the microcatheter. (a) White arrows point to the microcatheter tip. (b) The curve represents the path of the microcatheter tip in the sequence of fluorograms.

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:

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

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

where

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

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

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:

$$SNR = \frac{\bar{S} - \bar{B}}{SD} \quad (10)$$

where, \bar{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

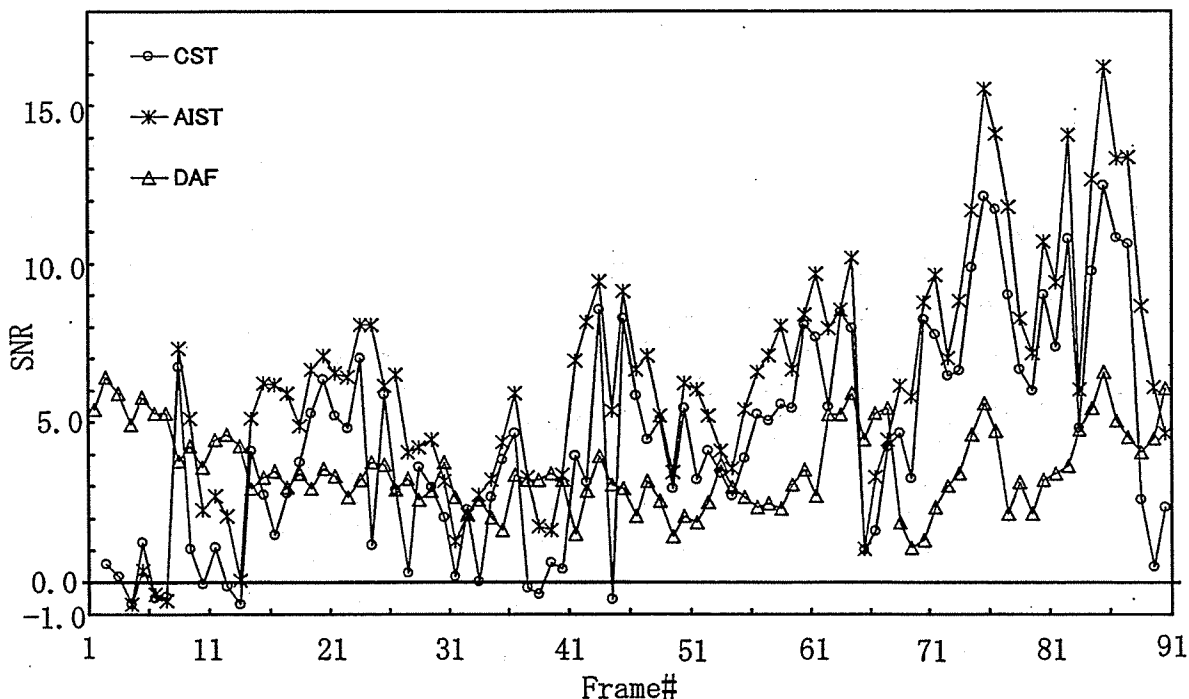


Fig 3. Variation of SNR for the three techniques. The AIST yields the best results, i.e., highest average SNR, whereas the DAF yields the lowest SD of the SNR values.

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), \bar{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.

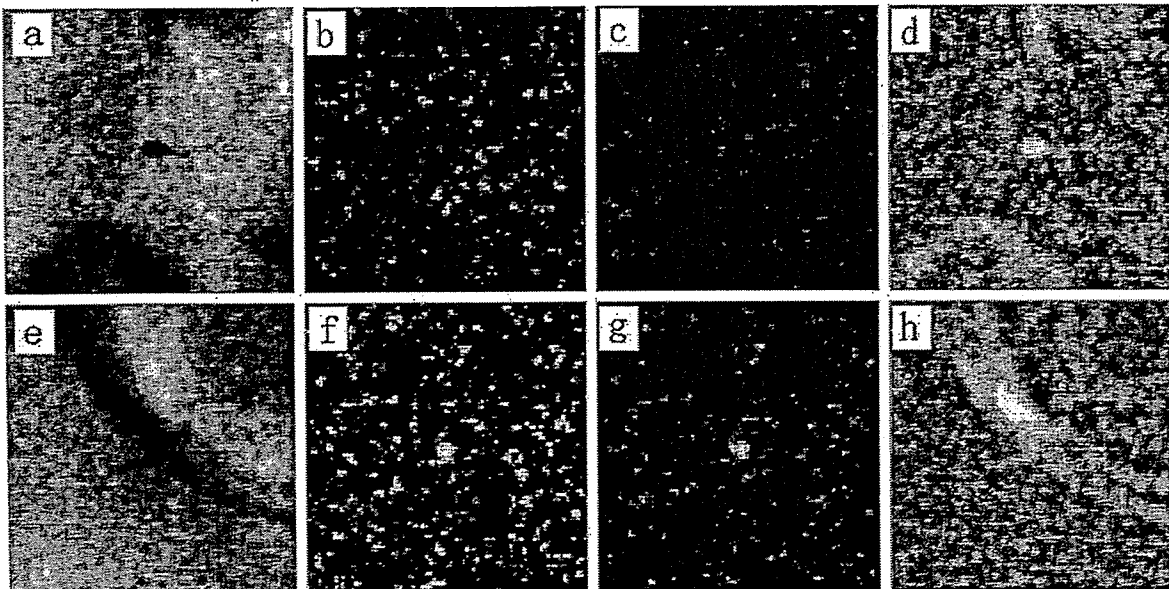


Fig 4. Examples of the original images and the images processed by the three techniques. (a) Original image of frame number seven in the sequential fluorograms. The images resulted from CST (b), AIST (c), and DAF (d). The image of the 7th frame is one of the images in which the catheter tip was not moved, 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.

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REFERENCES

1. Buecker A, Neuerburg JM, Adam GB, et al.: Real-time MR fluoroscopy for MR-guided iliac artery stent placement. *J Magn Reson Imaging* 12:616-622, 2000
2. Dion YM, Kadi BEH, Boudoux C, et al.: Endovascular procedures under near-real-time magnetic resonance imaging guidance: an experimental feasibility study. *J Vasc Surg* 32:1006-1014, 2000
3. Salem RR, Ward BA, Ravikumar TS: A new peripherally implanted subcutaneous permanent central venous access device for patients requiring chemotherapy. *J Clin Oncol* 11:2181-2185, 1993
4. Quick HH, Ladd ME, Nanz D, et al.: Vascular stents as RF antennas for intravascular MR guidance and imaging. *Magn Reson Med* 42:738-745, 1999
5. Quick HH, Kuehl H, Kaiser G, et al.: Interventional MR angiography with a floating table. *Radiology* 229:598-602, 2003
6. Kuehne T, Saeed M, Higgins CB, et al.: Endovascular stents in pulmonary valve and artery in swine: feasibility study of MR imaging-guided deployment and postinterventional assessment. *Radiology* 226:475-481, 2003
7. Strother CM, Unal O, Frayne R, et al.: Endovascular treatment of experimental canine aneurysms: feasibility with MR imaging guidance. *Radiology* 215:516-519, 2000
8. Wittkamp FH, Wever EF, Derksen R, et al.: Accuracy of the LocaLisa system in catheter ablation procedures. *J Electrocardiol* 32 (Suppl 7): 12, 1999
9. Starkhammar H, Bengtsson M, Kay DA: Cath-Finder catheter tracking system: a new device for positioning of central venous catheters. Early experience from implantation of brachial portal systems. *Acta Anaesthesiol Scand* 34:296-300, 1990
10. Meyer SA, Wolf PD: Registration of three-dimensional cardiac catheter models to single-plane fluoroscopic images. *IEEE Trans Biomed Eng* 46:1471-1479, 1999
11. Hoffmann KR, Esthappan J: Determination of three-dimensional positions of known sparse objects from a single projection. *Med Phys* 24:555-564, 1997
12. Baert SAM, van de Kraats EB, van Walsum T, et al.: Three-dimensional guide-wire reconstruction from biplane image sequences for integrated display in 3-D vasculature. *IEEE Trans Med Imag* 22:1252-1258, 2003
13. Baert SAM, Viergever MA, Niessen WJ: Guide-wire tracking during endovascular interventions. *IEEE Trans Med Imag* 22:965-972, 2003
14. Palti-Wasserman D, Brukstein AM, Beyar RP: Identifying and tracking a guide wire in the coronary arteries during angioplasty from X-ray images. *IEEE Trans Biomed Eng* 44:152-164, 1997
15. Takemura A, Harauchi H, Suzuki M, et al.: An algorithm for mapping the catheter tip position on a fluorograph to the three-dimensional position in magnetic resonance angiography volume data. *Phys Med Biol* 48:2697-2711, 2003
16. Sen A, Lan L, Doi K, et al.: Quantitative evaluation of vessel tracking techniques on coronary angiograms. *Med Phys* 26:698-706, 1999