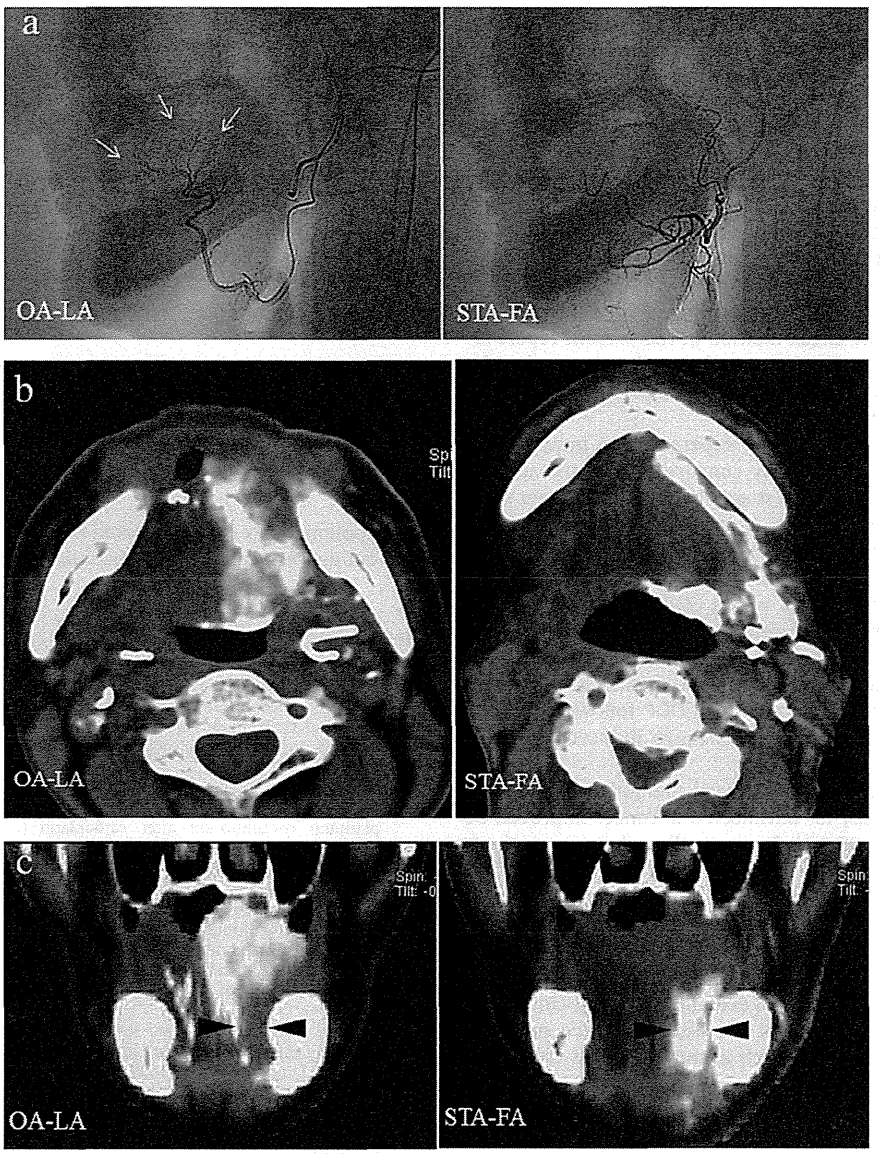

Fig. 3. Squamous cell carcinoma of the tongue (T4aN1M0). (a) Digital subtraction angiograms (DSA) of retrograde superselective intra-arterial infusion. Two catheters were superselectively inserted into the left lingual artery (LA) via the occipital artery (OA–LA) and left facial artery (FA) via the superficial temporal artery (STA–FA). Tumor stain is seen with the use of contrast medium on flow check DSA (OA–LA: arrowhead). (b, c) Axial and coronal views of angio-CT. The left side of the tongue tumor extends to the floor of the mouth and extrinsic muscles of the tongue. Angio-CT images showed that tumor staining of left tongue from left LA and left mouth floor from left FA can be seen with the use of contrast medium. The perfusion area from the left LA was not visible to the floor of the mouth and inside the mandible (c: OA–LA arrow), the perfusion area of floor of the mouth and inside the mandible was seen from the left FA (c: STA–FA arrow).

(21.4%), fever in 9 cases (8.0%), and renal failure occurred in 1 case (0.9%). Renal toxicity was significantly low: this finding is thought to be due to the low dose of CDDP and the STS-based neutralization of CDDP. No patients died as a result of treatment toxicity.

Discussion

Intra-arterial administration of anticancer agents might result in increased levels of anticancer agents being delivered to tumors and more potent antitumor effects compared to intravenous administration [3]. Present strategies at our institution for patients with locally advanced oral cancer include avoiding extended surgery and preserving primary organ function using retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy. This method has been performed since 1996 for organ preservation and improvement of treatment results in patients with advanced head and neck cancer [7]. For patients with N2 and N3 cervical lymph node metastases, retrograde superselective intra-arterial CRT combined with hyperthermia was utilized [9].

In cases of locally advanced tongue carcinoma (T3 and T4), the primary tumor extends to the floor of the mouth, lower gingiva and/or extrinsic muscle of the tongue. In such cases, the catheter must be placed in both the lingual and facial arteries. After catheterization, it is necessary to check the flow to the tumor on DSA (Fig 3a) and angio-CT (Fig 3b and c). Determining whether arterial infusion of an anticancer drug actually permeates the entire tumor is important for successful arterial infusion therapy. Angio-CT images were obtained in 5-mm-thick continuous sections in two

planes (axial and coronal) depending on the extent of the tumor. Angio-CT images showed that the perfusion area from the left lingual artery was not visible to the floor of the mouth and the inside of the mandible with use of contrast medium (Fig 3b and c: OA-LA). On the other hand, the perfused area on the floor of the mouth and inside the mandible was seen from the left facial artery (Fig 3b and c: STA-FA). Therefore, the position of the catheter must be checked to ascertain of the catheter was put in the proper position after catheterization. However, flow check angio-CT has sometimes difficulty to confirm the tumor feeding area due to the artifacts of crowned teeth. Nakamura et al. used MRI to ascertain the area reached by infusion of an arterial anticancer drug instead of angio-CT [10]. The MRI flow check method in the present report allows acquisition of images from various directions, thereby delineating the perfusion area by arterial infusion more accurately than conventional methods.

In the present trial of retrograde superselective intra-arterial DOC/CDDP chemotherapy and daily concurrent radiotherapy, OS and LC rates among patients with stage III and IV oral cancer were excellent. DOC enhances the effect of radiotherapy by causing cell synchronization at the most radiosensitive phase of the cell cycle (G2/M). CDDP enhances radiosensitivity through inhibition of DNA repair. The mechanisms by which CDDP and DOC serve as either a cytotoxic agent or radiosensitizer are distinct from each other [11]. DOC treatment followed by CDDP demonstrates a synergistic effect on cell survival inhibition, with increased intracellular platinum accumulation compared to CDDP followed by DOC, and DOC improves the multidrug resistance induced by single treatment with CDDP [12].

Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy for advanced oral cancer improved OS and LC rates. Five-year OS rate for stage III oral cancer patients was significantly higher than that for stage IV oral cancers ($P = 0.033$), 21 of 30 patients died due to the pulmonary metastasis; 18 of stage IV patients, 3 of stage III patients. On the other hand, 5-year LC rates for stage III and stage IV oral cancer patients were not significantly different ($P = 0.120$), indicating that this method provided good local control even for locally advanced oral cancer. These results suggest that the disease can be managed without a primary surgical approach in most patients with stage III and IV oral cancer.

In the present study, grade 3 or 4 toxicities included mucositis in 103 cases (92.0%) and grade 3 dysphagia with severe mucositis during treatment in 81 cases (72.3%). Intra-arterial chemotherapy can deliver a high dose of anticancer agents to head and neck lesions, and mucositis is a significant toxicity that can affect swallowing function. Thus, dysphagia is likely to improve with time in most cases within 3 months: in the present study only one patient was dependent on tube feeding over 1 year. Newman et al. [13] investigated swallowing and speech function after treatment for head and neck cancer with intra-arterial versus intravenous CRT, and found no statistically significant differences between the intra-arterial CRT group and the systemic CRT group in relation to swallowing function. Speech function was comparable; however, it was significantly worse in the intra-arterial CRT group than in the systemic CRT group. The present method was not associated with any major complications during follow-up, and no patients died as a result of treatment toxicity. These findings indicate that retrograde superselective intra-arterial CRT is safe and suitable for advanced oral cancer.

Multiple trials, particularly those using high-dose CDDP (RADPLAT), have reported a high response rate intra-arterial CRT [14]. On the other hand, a previous multicenter randomized phase 3 trial covering 239 patients with advanced unresectable head and neck cancer in the Netherlands concluded that CDDP-based intra-arterial CRT was not superior to intravenous CRT in relation to locoregional control and survival [15]. Robbins had questioned if this randomized trial was related to the technique used to deliver the intra-arterial infusions [16]. To prove the effectiveness and feasibility of retrograde intra-arterial CRT, further randomized trials comparing retrograde intra-arterial and intravenous chemotherapy combined with concurrent radiation therapy are necessary.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

We appreciate advice from Dr. Itaru Sato regarding statistical analysis, help from Dr. Kei Sugiura in providing patient data, and support from staff members at Yokohama City University.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.03.005.

References

[1] Salama JK, Seiwert TY, Vokes EE. Chemoradiotherapy for locally advanced head and neck cancer. J Clin Oncol 2007;25:4118–26.
[2] Robbins KT, Storniolo AM, Kerber C, et al. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. Head Neck 1992;14:364–71.
[3] Tohnai I, Fuwa N, Hayashi Y, et al. New superselective intra-arterial infusion via superficial temporal artery for cancer of the tongue and tumour tissue platinum concentration after carboplatin (CBDCA) infusion. Oral Oncol 1998;34:387–90.
[4] Fuwa N, Kodaira T, Furutani K, et al. A new method of selective intra-arterial infusion therapy via the superficial temporal artery for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:783–9.
[5] Iwai T, Fuwa N, Hirota M, et al. Secure surgical method for catheter placement via the occipital artery to achieve retrograde superselective intra-arterial chemotherapy for advanced oral cancer: Alternative to approach via the superficial temporal artery. Indian J Otolaryngol Head Neck Surg 2012, in press.
[6] Fuwa N, Kodaira T, Furutani K, et al. Intra-arterial chemoradiotherapy for locally advanced oral cavity cancer: analysis of therapeutic results in 134 cases. Br J Cancer 2008;98:1039–45.
[7] Mitsudo K, Shigetomi T, Fujimoto Y, et al. Organ preservation with daily concurrent chemoradiotherapy using superselective intra-arterial infusion via a superficial temporal artery for T3 and T4 head and neck cancer. Int J Radiat Oncol Biol Phys 2011;79:1428–35.
[8] Sobbin LH, Wittekind C, editors. International union against cancer. TNM classification of malignant tumors. New York: Wiley-Liss; 2002. p. 25–9.
[9] Mitsudo K, Koizumi T, Iida M, et al. Thermochemoradiation therapy using superselective intra-arterial infusion via superficial temporal and occipital arteries for oral cancer with N3 cervical lymph node metastases. Int J Radiation Oncol Biol Phys 2012;83:e639–45.
[10] Nakamura T, Fuwa N, Takayama K, et al. A new method using MRI to delineate areas of head and neck cancer targeted by intra-arterial infusion via a superficial temporal artery. Oral Oncol 2011;47:387–90.
[11] Hill BT, Whelan DH, Shellard SA, et al. Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublines in vitro. Invest New Drugs 1994;12:169–82.
[12] Maeda S, Sugiura T, Saikawa Y, et al. Docetaxel enhances the cytotoxicity of cisplatin to gastric cells by modification of intracellular platinum metabolism. Cancer Sci 2004;95:679–84.
[13] Newman LA, Robbins KT, Logemann JA, et al. Swallowing and speech ability after treatment for head and neck cancer with targeted intraarterial versus intravenous chemoradiation. Head Neck 2002;24:68–77.
[14] Robbins KT, Kumar P, Harris J, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multi-institutional setting: results of Radiation Therapy Oncology Group Trial 9615. J Clin Oncol 2005;23:1447–54.
[15] Rasch CR, Hauptmann M, Schornagel J, et al. Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: results of a randomized phase 3 trial. Cancer 2010;116:2159–65.
[16] Robbins KT, Howell SB, Williams JS. Intra-arterial chemotherapy for head and neck cancer: is there a verdict? Cancer 2010;116:2068–70.

J Physiol Sci (2014) 64:177–183
DOI 10.1007/s12576-014-0309-8

ORIGINAL PAPER

Hyperthermia generated with ferucarbotran (Resovist®) in an alternating magnetic field enhances cisplatin-induced apoptosis of cultured human oral cancer cells

Itaru Sato · Masanari Umemura · Kenji Mitsudo · Mitomu Kioi · Hideyuki Nakashima · Toshinori Iwai · Xianfeng Feng · Kayoko Oda · Akiyoshi Miyajima · Ayako Makino · Maki Iwai · Takayuki Fujita · Utako Yokoyama · Satoshi Okumura · Motohiko Sato · Haruki Eguchi · Iwai Tohnai · Yoshihiro Ishikawa

Received: 27 January 2014 / Accepted: 20 February 2014 / Published online: 12 March 2014

Abstract Hyperthermia is a promising anti-cancer treatment in which the tissue temperature is increased to 42–45 °C, and which is often used in combination with chemotherapy or radiation therapy. Our aim in the present work was to examine the feasibility of combination therapy for oral cancer with cisplatin and hyperthermia generated with ferucarbotran (Resovist®; superparamagnetic iron oxide) in an alternating magnetic field (AMF). First, we established that administration of ferucarbotran at the approved dosage for magnetic resonance imaging provides an iron concentration sufficient to increase the temperature to 42.5 °C upon exposure to AMF. Then, we examined the effect of cisplatin combined with ferucarbotran/AMF-induced hyperthermia on cultured human oral cancer cells (HSC-3 and OSC-19). Cisplatin alone induced apoptosis of cancer cells in a dose-dependent manner, as is well known. However, the combination of cisplatin with ferucarbotran/AMF was significantly more effective than cisplatin alone. This result suggests that it might be possible to reduce the clinically effective dosage of cisplatin by administering it in combination with ferucarbotran/AMF-induced hyperthermia, thereby potentially reducing the incidence of serious cisplatin-related side effects. Further work seems justified to evaluate simultaneous thermo-chemotherapy as a new approach to anticancer therapy.

Keywords Ferucarbotran · Hyperthermia · Oral cancer · Anti-cancer effect · Cisplatin · Resovist®

Abbreviations

AMF	Alternating magnetic field
MNPs	Magnetic nanoparticles
MRI	Magnetic resonance imaging
SPIO	Superparamagnetic iron oxide

Introduction

Cancer cells are more vulnerable to increased temperature than normal cells [1]. Thus, hyperthermia is viewed as a promising approach in cancer therapy [2]. Many techniques have been reported to increase the temperature of cancer tissues, such as whole-body hyperthermia [3], radiofrequency hyperthermia [4], microwave-induced hyperthermia [5], and implantable needles [6]. However, with all

I. Sato · M. Umemura (✉) · X. Feng · K. Oda · A. Miyajima · A. Makino · M. Iwai · T. Fujita · U. Yokoyama · Y. Ishikawa (✉)
Cardiovascular Research Institute, Yokohama City University, Graduate School of Medicine, 3-9 Fukuura, Yokohama 236-0004, Japan
e-mail: umemurma@yokohama-cu.ac.jp

Y. Ishikawa
e-mail: yishikaw@med.yokohama-cu.ac.jp

I. Sato · K. Mitsudo · M. Kioi · H. Nakashima · T. Iwai · I. Tohnai
Department of Oral and Maxillofacial Surgery, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Yokohama 236-0004, Japan

S. Okumura
Tsurumi University School of Dental Medicine, Tsurumi 230-8501, Japan

M. Sato
Department of Physiology, Aichi Medical University, Nagakute 480-1195, Aichi, Japan

H. Eguchi
Advanced Applied Science Department, Research Laboratory, IHI Corporation, Yokohama 235-8501, Japan

these modalities, it remains difficult to increase the temperature of only the cancer tissues in a controlled manner without damaging surrounding normal tissues.

More than 40,000 people are diagnosed with oral cancer, including cancers of the mouth, tongue, tonsils, and throat, every year in the US alone. Oral cancer can cause functional damage and disfigurement, and, in its advanced stages, it invades surrounding organs, causing disorders of speech, swallowing, and even chewing. Surgery may have serious adverse effects, so chemotherapy or radiation therapy is often favored in oral cancer patients, not with standing potentially serious systemic side effects. Hyperthermia is often preferred, e.g., for metastatic N3 cervical lymph nodes, because it has fewer adverse side effects. However, it is difficult to induce hyperthermia in a metastatic node-specific manner. Nevertheless, selective hyperthermia has been studied as a possible approach to obtain tumor-specific cytotoxicity, e.g., by ferromagnetic embolization [7]. More recently, magnetic nanoparticles (MNPs) have been investigated for this purpose, because MNPs generate heat when they are exposed to an alternating magnetic field (AMF) as a result of hysteresis and relaxational losses [8].

Ferucarbotran (Resovist®) is an organ-specific contrast agent used in magnetic resonance imaging (MRI) of local tumors, and the permissible dose in humans has been established by at least two studies [9, 10]. Because ferucarbotran consists of superparamagnetic iron oxide (SPIO) coated with carboxydextran, it generates heat when it is exposed to an AMF [11, 12], and it has been reported to induce selective hyperthermia when used in arterial embolization [11]. However, it has not been established whether ferucarbotran is suitable for inducing hyperthermia in cancer treatment.

Cisplatin (*cis*-diaminedichloroplatinum II; CDDP) is widely used in chemotherapy in many types of cancer, including oral cancers [13]. However, it has serious side effects, including acute kidney damage and/or renal failure [14–16]. Recent studies have demonstrated that hyperthermia stimulates cellular uptake of cisplatin [17, 18] and consequently enhances the cytotoxicity of cisplatin in cancer cells, both in vitro and in vivo [19–21]. Thus, combined treatment with cisplatin plus hyperthermia may allow the effective dose of cisplatin to be decreased sufficiently to minimize serious side effects.

Accordingly, in order to examine the feasibility of using combination therapy with cisplatin and ferucarbotran/AMF-induced hyperthermia in the therapy of oral cancer, in this study we examined the effect of the combined treatment on oral cancer cells in culture. Our results confirmed that ferucarbotran/AMF-induced hyperthermia significantly enhances the effect of cisplatin. Because both cisplatin and ferucarbotran have already been approved for clinical use, early introduction of this technique, at least for oral cancers, should be feasible.

Materials and methods

Reagent, drug and cell lines

Ferucarbotran (Resovist®) was purchased from FUJIFILM Pharma (Tokyo, Japan) [11]. Cisplatin was purchased from Wako Pure Chemical Industries (Osaka, Japan). Human oral squamous cell carcinoma cell lines OSC-19 and HSC-3 were purchased from the Japan Health Sciences Foundation, Health Science Research Resources Bank (Osaka, Japan). In all cases, cells from early passage cultures were stored and used for the experiments. OSC-19 and HSC-3 were cultured in Dulbecco's modified Eagle's medium (DMEM), 1 % penicillin–streptomycin, and 1 % L-glutamine.

Thermography

Thermal images were taken using a thermograph (infrared thermal imaging camera InfReC R300SR; Nippon Avionics, Tokyo, Japan). Temperature was also measured using a thermograph.

Alternating magnetic field (AMF) generator

An AMF was generated by a vertical coil with an inner diameter of 6.5 cm, driven by a transistor inverter (HOT SHOT; Ameritherm, New York, USA) operated at a

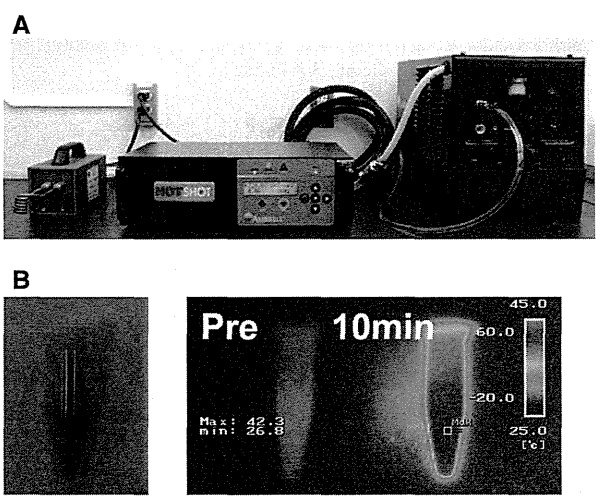

Fig. 1 Heat generation by ferucarbotran in an alternating magnetic field (AMF). **a** The alternating magnetic field (AMF) generator, **b** a photograph of ferucarbotran in medium (*left*), and thermal images of ferucarbotran in medium before (*middle*), and 10 min after AMF (308 kHz, EC 270 A) (*right*)

frequency of 308 kHz and electric current (EC) 250 A [12, 22–26]. Temperature was measured using a hand-held thermometer, HA-200 (Anritsu Meter, Tokyo, Japan).

Apoptosis assay

HSC-3 cells and OSC-19 (6×10^4 cells/well) were seeded on 6-cm dishes and incubated for 24 h. Cisplatin was then added to a concentration of 0 μM (control), 7.5 or 15 μM. When hyperthermia was to be applied, 10 mM ferucarbotran was added and AMF was performed with a HOT SHOT under the conditions described above [22, 25, 26]. Incubation was continued for 12 h at 37 °C, in an atmosphere of 5 % CO_2 in air. Cells were washed twice with cold PBS and suspended in 1× binding buffer at a concentration of 1×10^6 cells/ml. Next, a 100-μl aliquot of the solution, containing 1×10^5 cells, was transferred to a 5-ml culture tube. Then, 5 μl of allophycocyanin (APC) Annexin V and 5 μl of 7-aminoactinomycin D (AAD) (BD Biosciences, CA, USA) [27] were added to the tube. Incubation was continued for 15 min at room temperature (25 °C) in the dark. Finally, 400 μl of 1× binding buffer were added to each tube. Cells were examined by flow cytometry (BD FACSCanto II; BD Biosciences).

Cell cycle analysis

Cell cycle analysis was performed using The Cycletest™ Plus DNA Reagent Kit (BD Biosciences) according to the manufacturer's protocol [28]. Briefly, HCS-3 and OSC-19 cells treated with 0 μM (control), 7.5 or 15 μM cisplatin, with or without hyperthermia (10 mM ferucarbotan/AMF), were washed in PBS and fixed in 90 % ethanol. Fixed cells were washed twice in PBS and stained with 50 μM propidium iodide containing 5 μg/ml DNase-free RNase for 1 h, then analyzed by flow cytometry using a FACScan (BD FACSCanto II).

Statistical analysis

Data were analyzed using BD FACSDiva software (BD Biosciences). Data are expressed as mean ± SEM. Data were analyzed by one-way ANOVA followed by the Tukey post hoc test using GraphPad Prism software (GraphPad Software, CA, USA). The criterion of statistical significance was set at $p < 0.05$.

Results

Heat generation by ferucarbotran in an alternating magnetic field (AMF)

Heat production is determined by the magnetic properties of ferucarbotran, its concentration, and the strength of the AMF [12]. Therefore, we examined the heating effect of AMF on medium containing ferucarbotran by thermography (Fig. 1b). As shown in Fig. 2, the temperature increased time-dependently, and the extent of the increase was dependent on the concentration of ferucarbotran (Fig. 2a) and the magnitude of the EC used to generate AMF (Fig. 2b). The results showed that AMF produced at

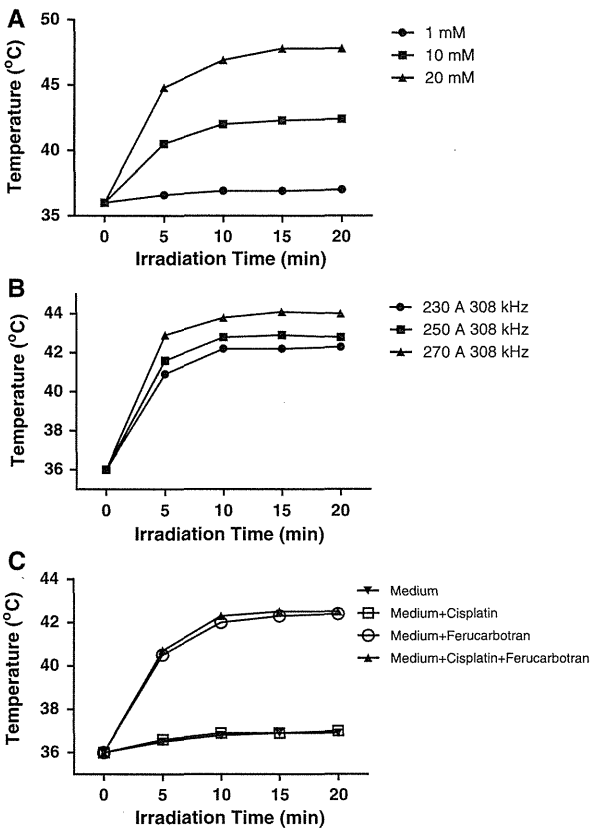

Fig. 2 Dependence of heat generation on ferucarbotran concentration and alternating magnetic field (AMF) strength. **a** Temperature–time curves at different concentrations of ferucarbotran (1, 10, or 20 mM equivalent of iron) on AMF at 308 kHz and EC 230 A. **b** Temperature–time curves in the presence of 10 mM ferucarbotran on AMF at different levels of electric current (230–270 A) at 308 kHz. **c** Effect of cisplatin (30 μM) on ferucarbotran (1, 10, or 20 mM equivalent of iron)/AMF (308 kHz, EC 230 A)-induced increase of temperature; medium only, medium + cisplatin, medium + ferucarbotran, and medium + cisplatin + ferucarbotran

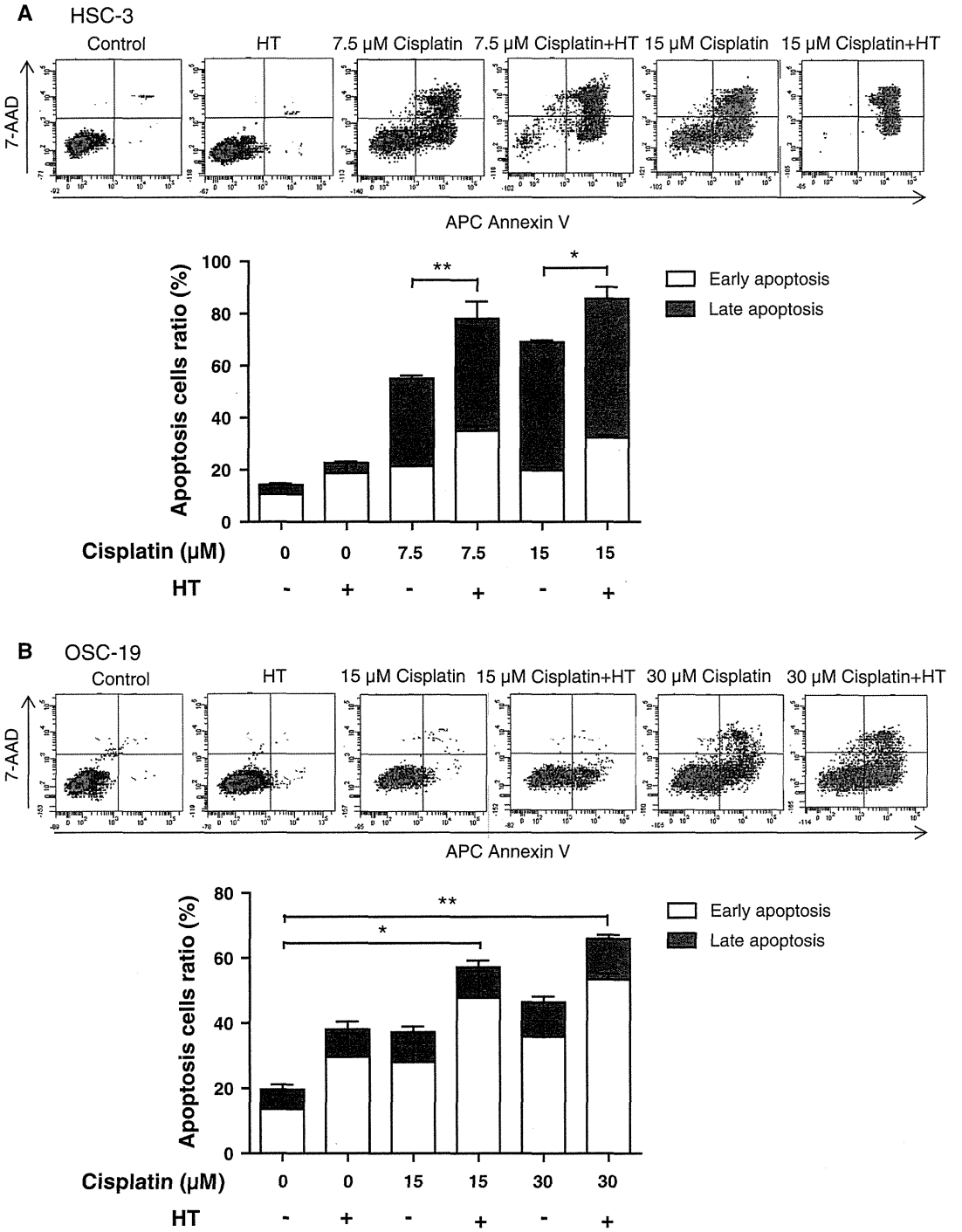

Fig. 3 Ferucarbotran/AMF-induced hyperthermia enhances the pro-apoptotic effect of cisplatin in human oral cancer cells. Annexin-V/PI staining of human oral cancer cells at 12-h intervals after treatment with 0, 7.5, or 15 μM cisplatin with or without hyperthermia (HT) in HSC-3 cells, and 0, 15, 30 μM cisplatin with or without HT in OSC-19 cells. **a** Representative analysis of apoptosis of HCS-3 cells and OSC-19 cells exposed to cisplatin and ferucarbotran with or without AMF. Annexin-V/PI method with FACS scan dot plot analysis was used to divide the treated and control cells into four groups: (1) living cells (*lower left quadrant*); (2) necrotic cells (*upper left quadrant*); (3) early apoptotic cells (*lower right quadrant*); and (4) late apoptotic cells (*upper right quadrant*). **b** Representative analysis of apoptosis of OSC-19 cells exposed to cisplatin with or without AMF. $*p < 0.05$, $**p < 0.01$; $n = 4$

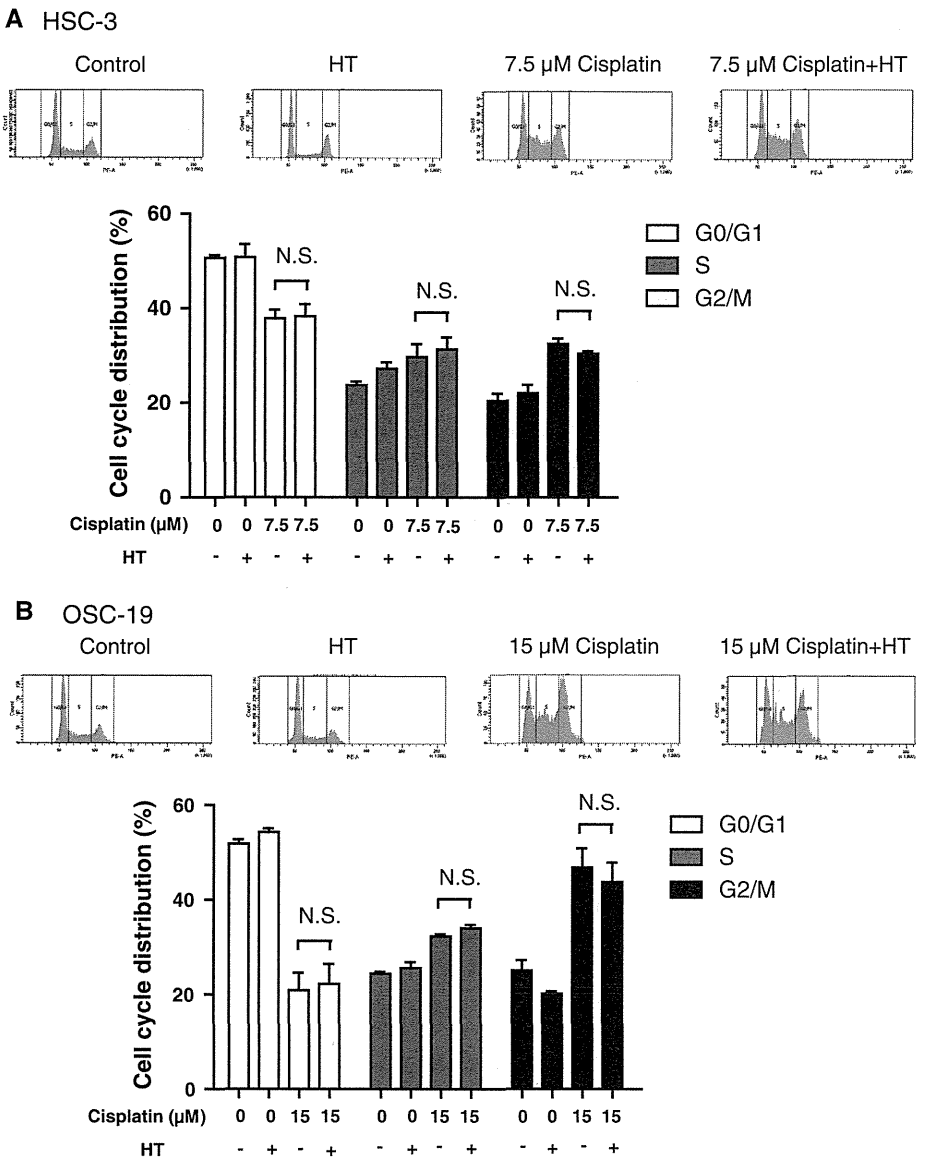

Fig. 4 Combination of cisplatin and ferucarbotran/AMF-induced hyperthermia causes G2/M arrest. Cell cycle analysis of HSC-3 and OSC-19 cells at 48-h intervals after treatment with 0, 7.5, or 15 μM of cisplatin with or without hyperthermia (HT). **a** Representative cell cycle analysis of HSC-3 cells in response to cisplatin treatment with or without AMF (*upper panel*) and of OSC-19 cells in response to cisplatin treatment with or without AMF (*lower panel*). *NS* not significant; $n = 4$

generator settings of 308 kHz and EC 250 A in the presence of 10 mM (equivalent of iron) ferucarbotran was sufficient to generate a temperature of 42.5 °C, and we adopted these conditions for the subsequent assays. We confirmed that cisplatin did not alter the heating effect under these conditions (Fig. 2c).

Ferucarbotran-enhanced cisplatin-mediated apoptosis

It has been reported that cisplatin induces apoptosis in cancer cells [29]. We thus examined whether ferucarbotran/AMF-induced hyperthermia further increased cisplatin-induced apoptosis in oral cancer cells. FACS analysis demonstrated that cisplatin increased both early and late apoptosis in a dose-dependent manner in HSC-3 cells (Fig. 3a) and OSC-19 cells (Fig. 3b). Ferucarbotran/AMF-induced hyperthermia for an hour significantly increased the apoptotic effect of cisplatin.

Cisplatin-induced G2/M arrest of human oral cancer cells was unaffected by hyperthermia

To examine whether hyperthermia modifies the mechanism of anti-cancer action of cisplatin, flow-cytometric cell-cycle analysis of treated cells was performed. Cisplatin induced potent G2/M arrest in both HSC-3 cells (Fig. 4a) and OSC-19 cells (Fig. 4b). We found that ferucarbotran/AMF-induced hyperthermia did not alter the effect of

cisplatin on the cell cycle. Thus, hyperthermia per se had no effect on the anti-cancer mechanism of cisplatin.

Discussion

Ferucarbotran is an organ-specific superparamagnetic contrast agent used in MRI, and its safety and maximum dosage (10 mM; 0.016 mL/kg, which contains 8 μmol (0.45 mg) Fe/kg equivalent of iron [30]) have been well established [9, 10]. Since hyperthermia has already been shown to enhance the anti-cancer effect of cisplatin [31] in the treatment of oral cancer, we anticipated that combination therapy with cisplatin and ferucarbotran/AMF-induced hyperthermia might be suitable for oral cancer treatment, making it possible to reduce the necessary dose of cisplatin and consequently reduce the risk of serious side effects.

Hyperthermia to induce apoptosis of cancer cells is best performed at about 42 °C, because temperatures above 44 °C have been reported to cause necrosis and damage to surrounding normal tissues [32]. Therefore, we first confirmed that the above concentration of ferucarbotran was sufficient to maintain a temperature of 42.5 °C under appropriate AMF conditions, and this level of hyperthermia could induce apoptosis of oral cancer cells, as evaluated by FACS analysis. It should be noted that it would still be necessary to optimize AMF conditions for clinical treatment. Similarly, it would be desirable to deliver cisplatin and ferucarbotran to oral cancer tissue in a selective manner. This may be achieved by the use of superselective intra-arterial infusion with a catheter, as we previously reported in oral cancer patients [33].

We previously reported that ROS production was higher in cancer cells than in normal cells, and was further increased when the temperature was increased [34]. Cisplatin also increases ROS production, and this is most likely the mechanism responsible for its anti-cancer effect [34, 35]. We confirmed that the combination of cisplatin and ferucarbotran/AMF-induced hyperthermia further enhanced ROS production (data not shown). This is important, because cisplatin may cause ototoxicity [36], so it is desirable to minimize the necessary cisplatin dose, as far as is consistent with therapeutic effectiveness, in the clinical context.

It is well known that cisplatin causes accumulation of cells in S phase and blocks the G0/G1 phases in xenografted human head and neck carcinoma cells [37], leading to apoptosis. [38, 39]. Our data showed that ferucarbotran/AMF-induced hyperthermia enhanced the anti-cancer effect of cisplatin without altering its characteristic effect on the cell cycle. Accordingly, ferucarbotran/AMF-induced hyperthermia did not appear to modify the mechanism of action of cisplatin in human oral cancer cells. Because both cisplatin and ferucarbotran are already in clinical use, we believe the combination of cisplatin with ferucarbotran/AMF-induced hyperthermia has the potential for early clinical application. It should at least be possible to reduce the clinically effective dosage of cisplatin by administering it in combination with ferucarbotran/AMF, thereby reducing the risk of serious cisplatin-related side effects. Further investigation seems warranted to confirm the safety and effectiveness of this combined treatment for oral cancers in humans.

Acknowledgments The authors are grateful to Akane Nagasako for technical assistance in this study. This work was supported in part by the Japan Society for the Promotion of Science (JSPS) (IS), as well as a Grant-in-Aid for JSPS Fellows (I.S.) from the Ministry of Health, Labor and Welfare of Japan (Y.I.), a Grant-in-Aid from the New Energy and Industrial Technology Development Organization of Japan (NEDO) (Y.I.), a Grant-in-Aid for Scientific Research on Innovative Areas (22136009) (Y.I.) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology of Japan (Y.I.), a grant from the IHI Corporation (H.E.), and a Grant for a Research and Development Project of Yokohama City University (Y.I.).

Conflict of interest The authors declare no potential conflicts of interest.

References

1. van der Zee J (2002) Heating the patient: a promising approach? Ann Oncol 13(8):1173–1184
2. Abe M, Hiraoka M, Takahashi M, Egawa S, Matsuda C, Onoyama Y, Morita K, Kakehi M, Sugahara T (1986) Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (Thermotron RF-8) in combination with radiation for cancer therapy. Cancer 58(8):1589–1595
3. Baba H, Clifton Stephens L, Strebel FR, Siddik ZH, Newman RA, Ohno S, Bull JMC (1991) Protective Effect of ICRF-187 against normal tissue injury induced by Adriamycin in combination with whole body hyperthermia. Cancer Res 51(13):3568–3577
4. Ikeda NHO, Kameda H, Ito H, Matsuda T (1994) Experimental study on thermal damage to dog normal brain. Int J Hyperth 10(4):553–561
5. Lin JCWY (1987) Interstitial microwave antennas for thermal therapy. Int J Hyperth 3(1):37–47
6. Stauffer PR, Cetas TC, Fletcher AM, Deyoung DW, Dewhirst MW, Oleson JR, Roemer RB (1984) Observations on the use of ferromagnetic implants for inducing hyperthermia. Biomed Eng, IEEE Trans 31(1):76–90
7. Barry JW, Bookstein JJ, Alksne JF (1981) Ferromagnetic embolization. Experimental evaluation. Radiology 138(2):341–349
8. Rosensweig RE (2002) Heating magnetic fluid with alternating magnetic field. J Magn Magn Mater 252:370–374
9. Reimer P, Balzer T (2003) Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. Eur Radiol 13(6):1266–1276
10. Hamm BST, Taupitz M, Maibauer R, Speidel A, Huppertz A, Frenzel T, Lawaczeck R, Wolf KJ, Lange L (1994) Contrast-enhanced MR imaging of liver and spleen: first experience in humans with a new superparamagnetic iron oxide. J Magn Reson Imaging 4(5):659–668

11. Takamatsu S, Matsui O, Gabata T, Kobayashi S, Okuda M, Ougi T, Ikehata Y, Nagano I, Nagae H (2008) Selective induction hyperthermia following transcatheter arterial embolization with a mixture of nano-sized magnetic particles (ferucarbotran) and embolic materials: feasibility study in rabbits. Radiat Med 26(4):179–187
12. Murase K, Oonoki J, Takata H, Song R, Angraini A, Ausanai P, Matsushita T (2011) Simulation and experimental studies on magnetic hyperthermia with use of superparamagnetic iron oxide nanoparticles. Radiol Phys Technol 4(2):194–202
13. Fram RJ (1992) Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 4(6):1073–1079
14. Arany I, Safirstein RL (2003) Cisplatin nephrotoxicity. Semin Nephrol 23(5):460–464
15. Meyer KBMN (1994) Cisplatin nephrotoxicity. Min Electrolyte Metab 20(4):201–213
16. Pabla N, Dong Z (2008) Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int 73(9):994–1007
17. Los G, Van Vugt MJH, Den Engelse L, Pinedo HM (1993) Effects of temperature on the interaction of cisplatin and carboplatin with cellular DNA. Biochem Pharmacol 46(7):1229–1237
18. Los G, van Vugt MJ, Pinedo HM (1994) Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. Br J Cancer 69(2):235–241
19. Barlogie B, Corry PM, Drewinko B (1980) In vitro thermochemotherapy of human colon cancer cells with *cis*-dichlorodiammineplatinum(II) and mitomycin C. Cancer Res 40(4):1165–1168
20. Cohen JD, Robins HI (1987) Hyperthermic enhancement of *cis*-Diammine-1,1-cyclobutane dicarboxylate platinum(II) cytotoxicity in human leukemia cells in vitro. Cancer Res 47(16): 4335–4337
21. Los GSP, Wondergem J, Mutsaers PH, Havemen J, ten Bokkel Huinink D, Smals O, Gonzalez-Gonzalez D, McVie JG (1991) Optimisation of intraperitoneal cisplatin therapy with regional hyperthermia in rats. Eur J Cancer 27(4):472–477
22. Wang X, Chen Y, Huang C, Wang X, Zhao L, Zhang X, Tang J (2013) Contribution of a 300 kHz alternating magnetic field on magnetic hyperthermia treatment of HepG2 cells. Bioelectromagnetics 34(2):95–103
23. Zhao QLW, Cheng R, Mao L, Arnold RD, Howerth EW, Chen ZG, Platt S (2012) Magnetic nanoparticle-based hyperthermia for head and neck cancer in mouse models. Theranostics 2(1):113–121
24. Atsumi T, Jeyadevan B, Sato Y, Tohji K (2007) Heating efficiency of magnetite particles exposed to AC magnetic field. J Magn Magn Mater 310(2):2841–2843
25. Hayashi KNM, Sakamoto W, Yogo T, Miki H, Ozaki S, Abe M, Matsumoto T, Ishimura K (2013) Superparamagnetic nanoparticle clusters for cancer theranostics combining magnetic resonance imaging and hyperthermia treatment. Theranostics 3(6):366–376
26. Nakao KOY, Akao Y, Ito Y, Marukawa O, Tachibana S, Kawakami M, Sasaki S (2000) The synergistic effects of hyperthermia and anticancer drugs on induction of apoptosis. Med Electron Microsc 33(1):44–50
27. Shao Y, Aplin AE (2010) Akt3-mediated resistance to apoptosis in B-RAF–targeted melanoma cells. Cancer Res 70(16): 6670–6681
28. Lee JT, Li L, Brafford PA, van den Eijnden M, Halloran MB, Sproesser K, Haass NK, Smalley KSM, Tsai J, Bollag G et al (2010) PLX4032, a potent inhibitor of the B-Raf V600E oncogene, selectively inhibits V600E-positive melanomas. Pigment Cell Melanoma Res 23(6):820–827
29. Al-Bahlani S, Fraser M, Wong AYC, Sayan BS, Bergeron R, Melino G, Tsang BK (2011) P73 regulates cisplatin-induced apoptosis in ovarian cancer cells via a calcium/calpain-dependent mechanism. Oncogene 30(41):4219–4230
30. Kopp AF, Laniado M, Dammann F, Stern W, Grönewäller E, Balzer T, Schimpfky C, Claussen CD (1997) MR imaging of the liver with Resovist: safety, efficacy, and pharmacodynamic properties. Radiology 204(3):749–756
31. Kusumoto TYM, Baba H, Takahashi I, Kusumoto H, Ohno S, Sugimachi K (1993) Sequence dependence of the hyperthermic potentiation of carboplatin-induced cytotoxicity and intracellular platinum accumulation in HeLa cells. Br J Cancer 68(2):259–263
32. Ito A, Honda H, Kobayashi T (2006) Cancer immunotherapy based on intracellular hyperthermia using magnetite nanoparticles: a novel concept of "heat-controlled necrosis" with heat shock protein expression. Cancer Immunol Immunother 55(3): 320–328
33. Mitsudo K, Koizumi T, Iida M, Iwai T, Oguri S, Yamamoto N, Itoh Y, Kioi M, Hirota M, Tohnai I (2012) Thermochemoradiation therapy using superselective intra-arterial infusion via superficial temporal and occipital arteries for oral cancer with N3 cervical lymph node metastases. Int J Radiat Oncol Biol Phys 83(5):639–645
34. Fukumura H, Sato M, Kezuka K, Sato I, Feng X, Okumura S, Fujita T, Yokoyama U, Eguchi H, Ishikawa Y et al (2012) Effect of ascorbic acid on reactive oxygen species production in chemotherapy and hyperthermia in prostate cancer cells. J Physiol Sci 62(3):251–257
35. Florea A-M, Büsselberg D (2011) Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers 3(1):1351–1371
36. Kim H-J, Lee J-H, Kim S-J, Oh GS, Moon H-D, Kwon K-B, Park C, Park BH, Lee H-K, Chung S-Y et al (2010) Roles of NADPH oxidases in cisplatin-induced reactive oxygen species generation and ototoxicity. J Neurosci 30(11):3933–3946
37. Jäckel M, Köpf-Maier P (1991) Influence of cisplatin on cell-cycle progression in xenografted human head and neck carcinomas. Cancer Chemother Pharmacol 27(6):464–471
38. Pucci B, Kasten M, Giordano A (2000) Cell cycle and apoptosis. Neoplasia 2(4):291–299
39. Aeq B (2004) Links between apoptosis, proliferation and the cell cycle. Br J Biomed Sci 61(2):99–102

Indian J Otolaryngol Head Neck Surg
(January 2014) 66(Suppl 1):S314–S315; DOI 10.1007/s12070-011-0369-5

SHORT COMMUNICATION

Variable Oral Device for Measuring Oral Lesions

Toshinori Iwai · Jiro Maegawa · Yoshiro Matsui · Kenji Mitsudo · Iwai Tohnai

Received: 9 July 2011 / Accepted: 15 November 2011 / Published online: 27 November 2011

Abstract We describe use of a variable oral device for efficient measurement of oral lesions.

Keywords Oral lesion · Measurement · Variable oral device

Precise size measurement of oral lesions is important not only for categorizing the T stage of oral malignancy but also for the follow-up of premalignant lesions such as leukoplakia or erythroplakia. In particular, T stage can influence the selection of treatment such as surgery or chemoradiotherapy. Although a straight measurement device or caliper is commonly used by head and neck surgeons, measurement of oral lesions is sometimes constrained by the space of the oral cavity, movement of the tongue and the physical complexity of anatomical structures. We describe here the use of a variable oral device for efficient measurement of oral lesions.

A variable oral device (Variable Oral Measure®, Four Medics, Tokyo, Japan) for measuring oral lesions was constructed according to our design. The device consists of a handle that attaches to one of four measurement scales (10, 20, 40 or 60 mm) via a ball and socket joint and can be used for deciding surgical margin (10 mm) and T stage (Fig. 1). In addition, each measurement scale can be easily exchanged with a different size, angled by 90° and rotated a full 360° around its axis (Fig. 2). Furthermore, the surface of the measurement scales is non-reflective, which is beneficial for taking oral photographs.

It is sometimes difficult to measure oral lesions, especially upper gingival lesions. However, our variable oral device enables efficient and precise measurement of lesion size because measurement scales are interchangeable and

T. Iwai (✉) · K. Mitsudo · I. Tohnai
Department of Oral and Maxillofacial Surgery, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Yokohama, Kanagawa 236-0004, Japan
e-mail: iwai104oams@yahoo.co.jp

J. Maegawa
Department of Plastic and Reconstructive Surgery, Yokohama City University Hospital, 3-9 Fukuura, Yokohama, Kanagawa 236-0004, Japan

Y. Matsui
Department of Oral and Maxillofacial Surgery, Faculty of Medicine, Kagawa University, 1750-1, Ikenobe, Kita-gun, Kagawa 761-0793, Japan

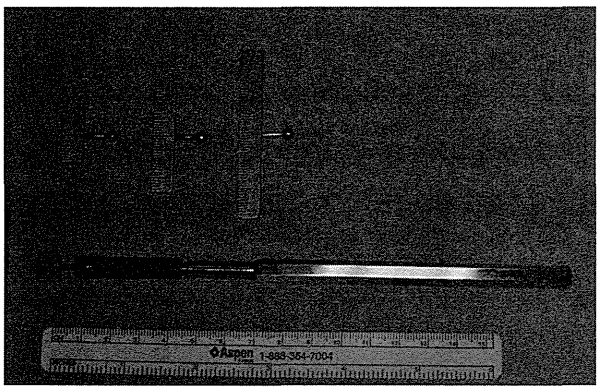

Fig. 1 The variable oral device

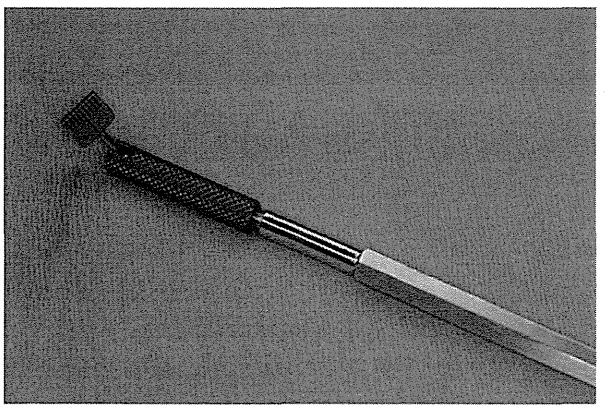

Fig. 2 Measurement scales are interchangeable, can be angles by up to 90° and rotated 360° on the axis of the handle

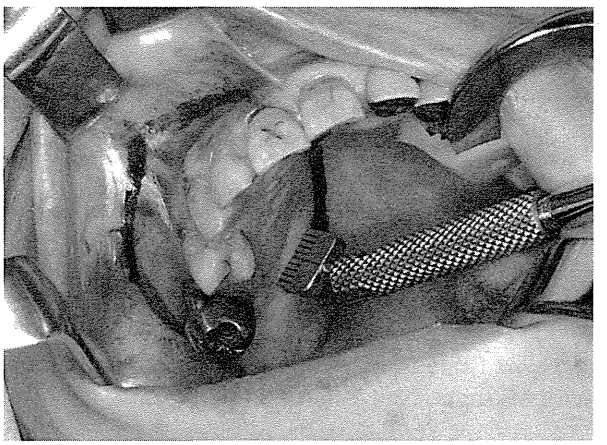

Fig. 3 Using the variable oral device for deciding surgical margin

adjustable. Therefore, multiple devices are no longer necessary. Moreover, using the variable oral device with the 10 mm measurement scale to determine surgical margin, regardless of lesion site, is quicker than using other measurement devices (Fig. 3). Therefore, we recommend the variable oral device for measuring the size of oral lesions and for deciding surgical margin.

Conflict of interest None.

Indian J Otolaryngol Head Neck Surg
(Apr–Jun 2014) 66(2):205–207; DOI 10.1007/s12070-012-0501-1

SHORT COMMUNICATION

Secure Surgical Method for Catheter Placement via the Occipital Artery to Achieve Retrograde Superselective Intra-Arterial Chemotherapy for Advanced Oral Cancer: Alternative to Approach via the Superficial Temporal Artery

Toshinori Iwai · Nobukazu Fuwa · Makoto Hirota · Kenji Mitsudo · Iwai Tohnai

Received: 17 August 2011 / Accepted: 3 February 2012 / Published online: 15 February 2012

Abstract We describe secure surgical method for catheter placement using ultrasonic scalpel via the occipital artery to achieve retrograde superselective intra-arterial chemotherapy for advanced oral cancer, as alternative to approach via the superficial temporal artery.

Keywords Catheter placement · Occipital artery · Retrograde superselective intra-arterial chemotherapy · Superficial temporal artery

For the treatment of advanced oral cancer, we generally perform superselective intra-arterial catheterization via the superficial temporal artery (STA) because of long-term catheterization and lower risk of cerebral infarction than Seldinger's method [1, 2]. More effective chemoradiotherapy is thus possible since catheter placement via STA enables continuous chemotherapy and daily concurrent radiotherapy [2]. However, retrograde superselective intra-arterial chemotherapy is not possible if the STA can not be used or if the catheter can not be placed into the target artery, for example, because of a thin-diameter vessel, meander of the external carotid artery, intraoperative laceration, or when previous intra-arterial chemotherapy has been performed. In such cases, the occipital artery (OA) offers another route [3]. Catheter placement via the OA is, however, difficult and not well-established because the OA is anatomically located in a deep region under the sternocleidomastoid muscle and splenius capitis muscle. The OA is generally identified by palpation of its pulsation, but the identification is time-consuming when palpation is difficult. Additionally, electrocautery for dissection of muscles has the potential to injure the OA and careful intervention is necessary. We describe here a newly developed method of secure catheter placement using ultrasonic scalpel via the OA to achieve retrograde superselective intra-arterial chemotherapy for the treatment of advanced oral cancer.

Institutional review board approval was obtained from Yokohama City University Hospital. Fourteen patients with squamous cell carcinoma of the tongue, buccal mucosa or floor of the mouth underwent catheter placement via the OA under local anesthesia. The exposure of the OA was achieved using an ultrasonic scalpel (Harmonic Scalpel, Ethicon Endo-Surgery, OH, USA) and Doppler ultrasound. Preoperatively, three-dimensional computed tomography angiography of the carotid artery was performed to identify the course of the external carotid artery and the relationship between the OA and the target artery such as the lingual artery and facial artery (Fig. 1). The OA was identified posterior of the mastoid process by Doppler ultrasound, and then a 3.5 cm skin incision was made and the sternocleidomastoid muscle and splenius capitis muscle were safely transected using the ultrasonic scalpel without the OA injury (Fig. 2). After exposure of the OA, a 0.016-inch guidewire (GT wire, Terumo Corp., Tokyo, Japan) was inserted into the common carotid artery through the OA. A vinyl hook-shaped catheter (NECK, 4 Fr in outer diameter, Medikit Corp., Tokyo, Japan) was inserted into the OA

T. Iwai (✉) · M. Hirota · K. Mitsudo · I. Tohnai
Department of Oral and Maxillofacial Surgery, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
e-mail: iwai104oams@yahoo.co.jp

N. Fuwa
Department of Radiation Oncology, Southern Tohoku Proton Therapy Centre, Southern Tohoku Research Institute of Neuroscience, 7-172 Yatsuyamada, Koriyama, Fukushima 963-8052, Japan

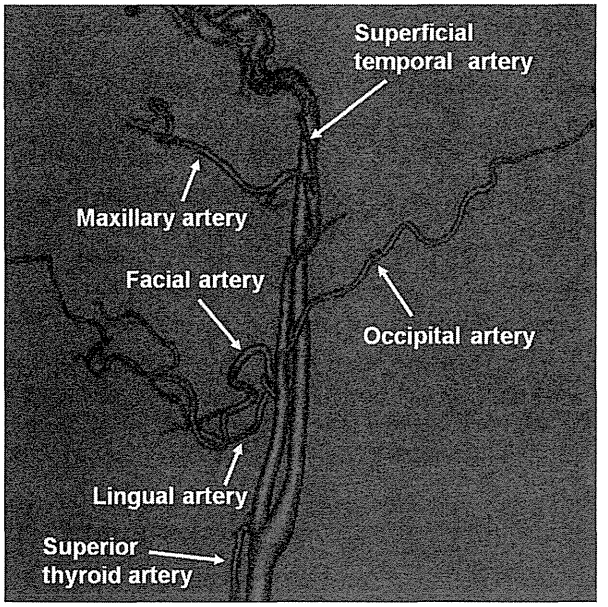

Fig. 1 Three-dimensional computed tomography angiography of the external carotid artery and its branch

along the guidewire and placed below the bifurcation of the target artery. The tip of catheter was then superselectively inserted into the target artery by drawing it back under fluoroscopic guidance, and the position of catheter was checked by injection of contrast medium and blue dye (Fig. 3). After that, the catheter was fixed to the OA with 3-0 silk. When the catheter was unstable or target artery is located distally from the OA, the guide-wire was inserted again into the catheter and replaced with a polyurethane straight catheter (ANTHRON P-U catheter; tapering type, 5 Fr in outer diameter, 2.7 Fr in outer diameter at the tip of the catheter, Toray Medical Corp., Tokyo, Japan) by the guide-wire exchange method. The transected muscles, subcutaneous tissues and skin were sutured. Finally, the catheter was fixed to the skin around the mastoid process.

The catheter could be placed superselectively to the target artery in all patients. Mean exposure time of the OA was 17.6 min, and mean operating time was 77.4 min. The mean exposure time of the OA in our series was considerably less than that in a previous report by Hasegawa et al. [3] (42 min) since we could identify the position of the OA easily using Doppler ultrasound and we used ultrasonic scalpel which achieves good hemostasis, minimizes injury to important structures and, in comparison with electrocautery, can reduce operative time, blood loss and drainage volume, and shows improved arterial blood flow [4, 5]. Three-dimensional vascular mapping, the use of Doppler ultrasound and ultrasonic scalpel offers a safe and reliable

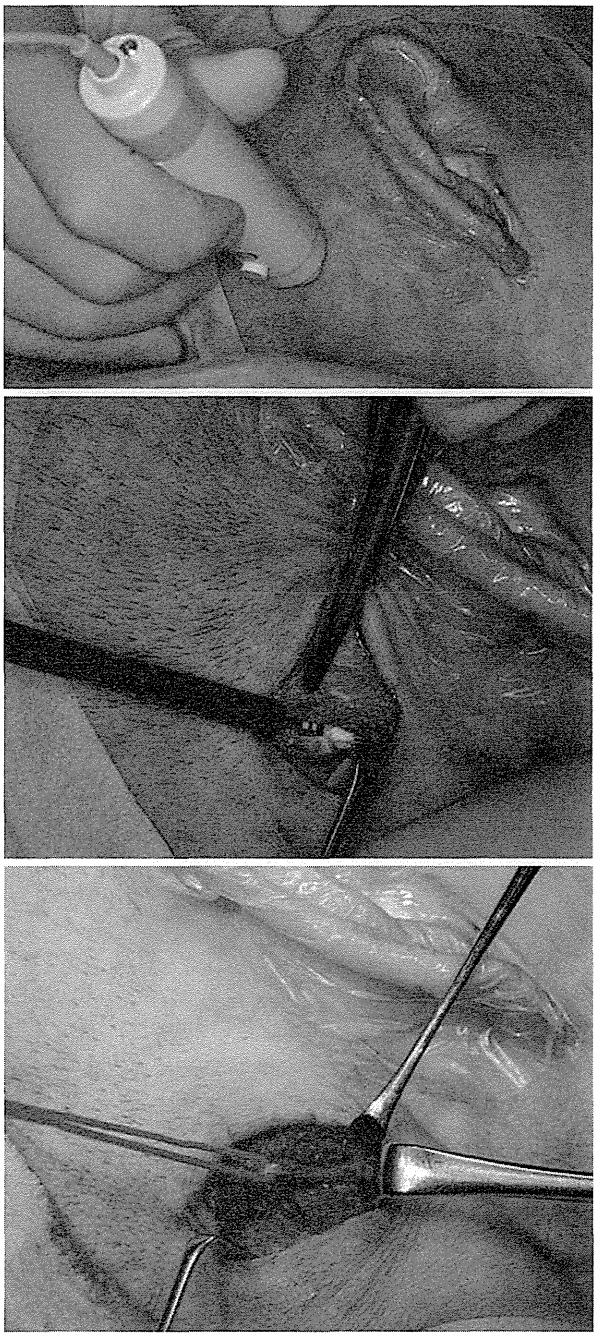

Fig. 2 Surgical approach for catheterization via the occipital artery

method for catheter placement via the OA that shortens the surgical time. In conclusion, this approach via the OA can be extended to the indication of retrograde superselective intra-arterial chemotherapy.

Conflict of interest None.

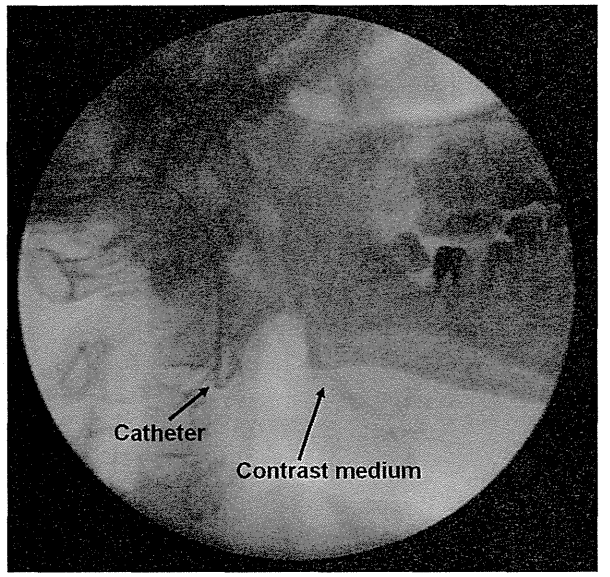

Fig. 3 Fluoroscopic view of catheter placement into target artery via the occipital artery

References

1. Tohnai I, Fuwa N, Hayashi Y, Kaneko R, Tomaru Y, Ueda M (1998) New superselective intra-arterial infusion via superficial temporal artery for oral cancer of the tongue and tumor tissue platinum concentration after carboplatin (CBDCA) infusion. Oral Oncol 34:387–390
2. Fuwa N, Kodaira T, Furutani K et al (2008) Intra-arterial chemoradiotherapy for locally advanced oral cavity cancer: analysis of therapeutic results in 134 cases. Br J Cancer 8:1039–1045
3. Hasegawa H, Kano M, Sato E et al (2008) Surgical method for catheter placement via the occipital artery by an approach from the posterior of the mastoid process. Int J Oral Maxillofac Surg 37:82–85
4. Deo S, Hazarika S, Shukla NK, Kar M, Samaiya A (2005) A prospective randomized trial comparing harmonic scalpel versus electrocautery for pectoralis major myocutaneous flap dissection. Plast Reconstr Surg 115:1006–1009
5. Erkut B, Unlu Y, Karapolat S et al (2008) Comparison of harmonic scalpel and high-frequency electrocautery in radial artery harvesting. J Cardiovasc Surg (Torino) 49:371–379

Correspondence from the JSTM

ハイパーサーミア現況調査 (2012) 報告書

一般社団法人日本ハイパーサーミア学会，健保・保険点数改定委員会
寺嶋　廣美 (原三信病院，放射線科)
大栗　隆行 (産業医科大学，放射線科)
今田　　肇 (戸畑共立病院，がん治療センター)
藤内　　祝 (横浜市立大学，顎顔面口腔機能制御学)
櫻井　英幸 (筑波大学，放射線腫瘍科)
武田　　力 (大阪がん免疫化学療法センター)
照沼　　裕 (東京クリニック)
谷川　啓史 (ビオセラクリニック)
近藤　元治 (千春会ハイパーサーミアクリニック)
田中　良明 (川崎幸病院，放射線治療センター)

理事長　大西　武雄 (奈良県立医科大学放射線腫瘍医学)

はじめに

1980 年代から始まった我が国のハイパーサーミアは，保険収載されたこともあって徐々に普及してきた．近年は治療施設や対象疾患は大きな変化を来たし，診療報酬の問題も大きくなっている．日本ハイパーサーミア学会，健保・保険点数改定委員会は，診療報酬の改定に向けて作業を続けてきた．その一環として 2012 年 3 月，全国の実情を調査するためアンケート調査を行った．その結果をまとめたので報告する．

1．アンケート配布と回収率

平成 24 年 3 月 19 日，アンケート調査票を全国 84 施設に電子メールで配信した．そのうち 44 施設から回答があり，回収率 (44/84) は 52.4%，有効回答率 (42/84) は 50%となった．

2．調査結果

2-1．加温機器の機種

現在，国内の温熱治療装置として稼働しているタイプは表在近傍から深部まで加温できる RF 波加温装置と表在加温のマイクロ波加温装置がある．前者が 42 施設，後者が 2 施設の稼働であった．(この項のみ回答 44 施設)

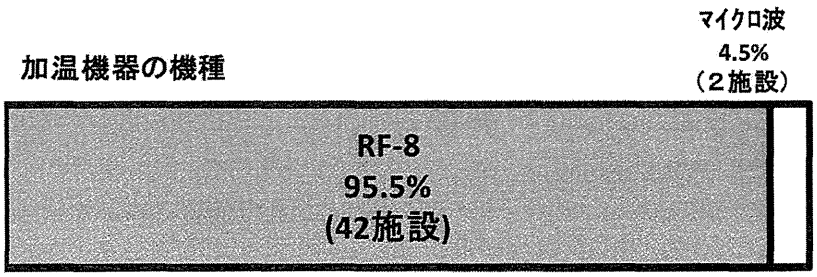

図 1．RF 波温熱治療装置とマイクロ波温熱治療装置の設置比率

2－2．温熱治療装置の新規導入時期

温熱治療装置は 30 年ほど前，全国に設置が拡大した，その後，稼働要員や治療時間の課題等から設置台数は減少傾向を示した．その後，2000 年以降，化学療法及び放射線療法等との併用療法の有用性が認められるようになると徐々に設置台数が増加した．

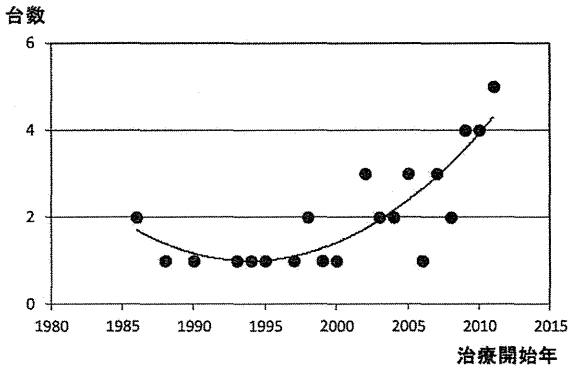

図 2．温熱治療装置の年度別新規設置台数の推移

2－3．温熱治療の患者数と運営費

この 5 年間 (2007～2011 年) の温熱治療装置稼働に伴う①治療患者総数，②平均治療回数/人，③治療関係人件費，④治療関係事務・運営費，⑤治療関係施設費について調査した．その結果は，今後の温熱治療部門の運営に活用できる．調査項目①～⑤の結果の一覧を表 1 に示す．

表 1．温熱治療装置稼働に伴う費用等

調 査 項 目	年 (年度)				
	2007	2008	2009	2010	2011
治療患者総数	3,195	3,561	4,784	8,868	12,077
平均治療回数/人	11.8	12.1	10.9	11.2	10.7
治療関係人件費 (千円)	3,906	4,268	5,048	11,250	10,119
治療関係事務・運営費 (千円)	1,913	2,184	2,310	2,772	5,221
治療関係施設費 (千円)	6,178	6,709	6,717	9,851	10,075

① 温熱治療患者数の推移

温熱治療患者数は 2009 年から大きく増加し，2007 年比，2011 年は 4 倍程度まで拡大している．しかし，本設問のアンケート結果には温熱治療患者総数と温熱治療患者延べ人数が混在している可能性がある．(この項，施設により統計が大きく異なる数値)

② 平均治療回数/人

患者一人あたりの平均治療回数は，数回程度から 40 回程度まで施設間の開きは大きかった．治療回数の平均値は各年とも 11 回前後であり大きな変動はなかった．

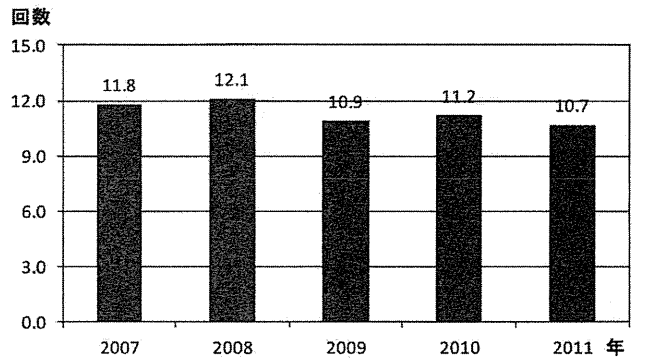

図 3．患者一人あたりの平均治療回数

③ 治療関係人件費

治療関係人件費は 2007 年比で 2011 年は 2.5 倍ほどになっている．

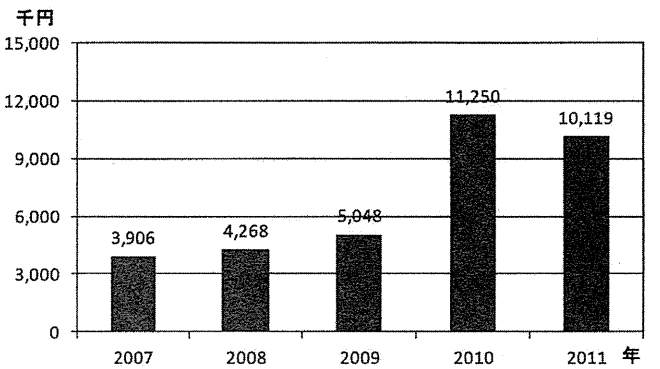

図 4．治療関係人件費

④ 治療関係事務・運営費

人件費と連動し事務費・運営費も増加している.

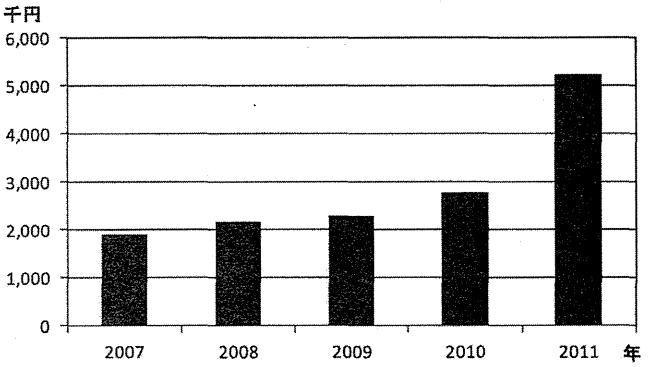

図 5 . 治療関係事務・運営費

⑤ 治療関係施設費

本費用は装置本体や建物等に相当し 2010 年ごろから増加傾向になっている. 2007 年比, 2011 年は 1.6 倍程度になっている.

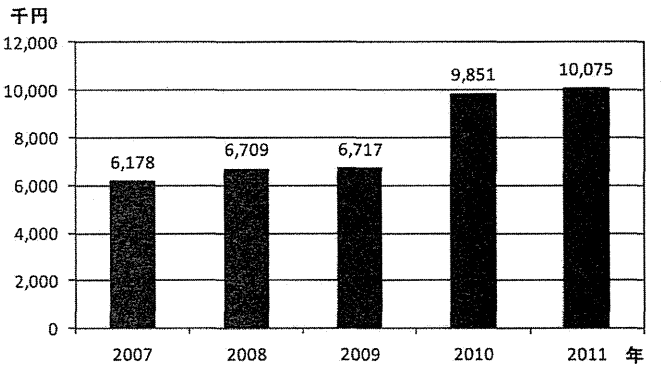

図 6 . 温熱治療関係施設費

2－4 . 温熱治療対象疾患別の治療患者数と治療評価

調査結果を示す. なおアンケート調査項目にない分類で報告されたものは, 「(その他) 設問以外の回答」に記載して集計に取り込んだ.

① 対象疾患ごとの年度別患者推移

表 2．温熱治療対象疾患の治療数の推移

温熱治療対象疾患	年 (年度)				
	2007	2008	2009	2010	2011
頭頸部がん	63	60	75	90	103
肺がん	247	319	382	493	454
縦隔腫瘍	8	6	17	20	26
乳がん	120	144	167	177	165
食道がん	50	77	89	106	98
肝臓がん	137	261	201	294	300
すい臓がん	129	207	296	341	404
胃がん	156	159	245	309	286
結腸・直腸がん	230	305	289	347	323
卵巣がん	54	75	83	100	132
子宮頸がん	43	67	71	65	62
軟部組織腫瘍	22	16	35	75	20
転移性がん	214	391	545	1,044	1,165
再発がん	90	74	91	98	80
その他のがん	69	96	100	81	131
(その他) 設問以外の回答					
悪性リンパ腫	6	8	12	22	4
胆道 (胆管・胆嚢) がん	35	59	75	65	70
泌尿器がん	6	12	12	7	21
他の婦人科がん	2	4	8	13	20
十二指腸・小腸がん	3	4	5	5	5
皮膚がん	5	5	7	5	4
膀胱・尿管がん	7	9	10	15	18
腎がん	7	6	7	19	15
前立腺がん	41	35	57	114	85
回腸がん				1	
胆管細胞がん				3	1
腹膜播種		1			4
脂肪肉腫					1
骨転移	10	2	0	3	5
総　　数	1,754	2,402	2,879	3,912	4,002

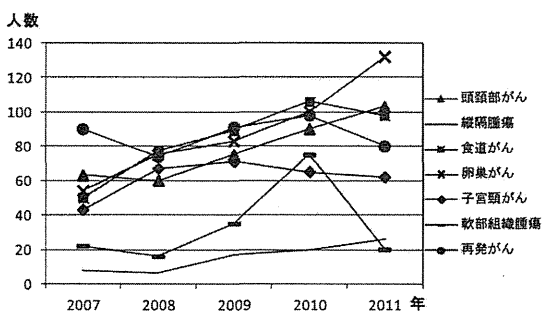

図 7－1．対象疾患ごとの患者数推移

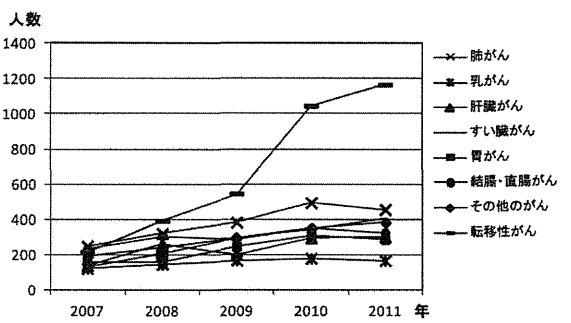

図 7－2．対象疾患ごとの患者数推移

② 対象疾患の治療評価

対象疾患の治療評価は 5 段階評価がされた施設のデータのみ使用した.

＊ 5 段階評価 (U：評価不能, CR：著効, PR：有効, SD：不変, PD：増悪)

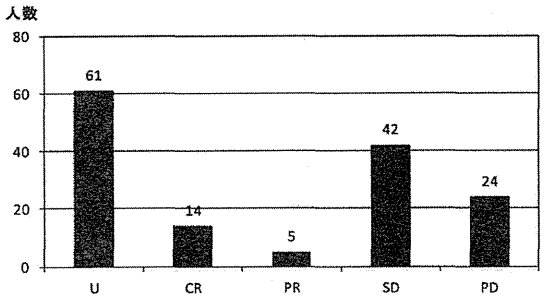

図 8 . 頭頸部がん

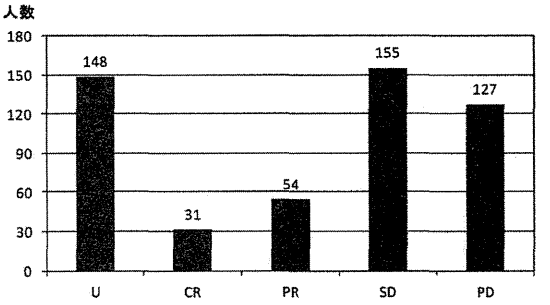

図 9 . 肺がん

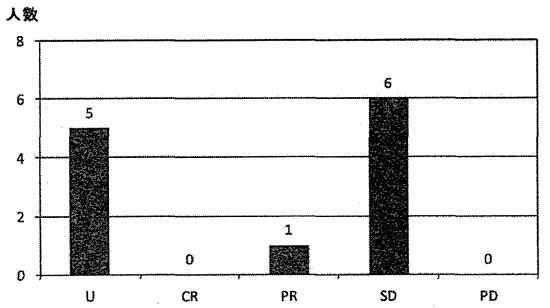

図10. 縦隔腫瘍

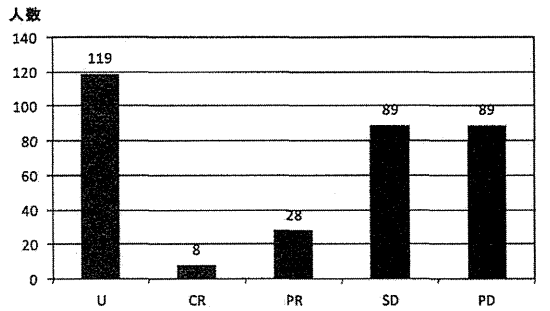

図11. 乳がん

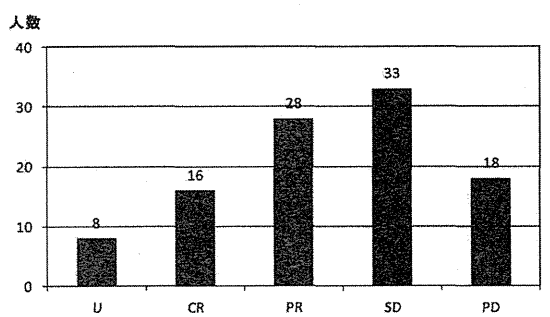

図12. 食道がん

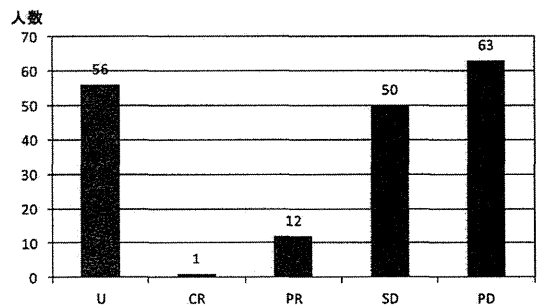

図13. 肝がん

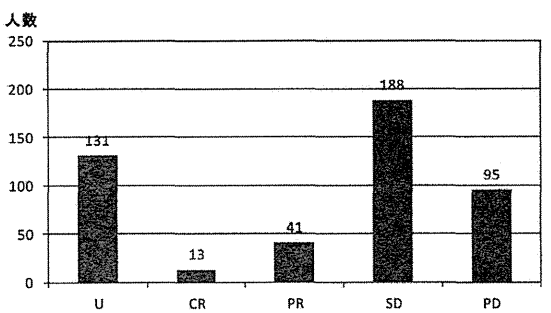

図14. すい臓がん

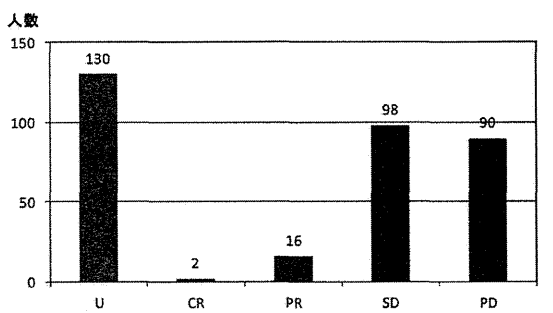

図15. 胃がん