Review

# Clinical Results of Systemic Chemotherapy Combined with Regional Hyperthermia

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Abstract: Hyperthermia (HT) can be directly cytotoxic to cancer cells, and can also act as a radiation-sensitizer and chemo-sensitizer. Although the combination of HT with radiotherapy has been the primary focus for research, there is an equally strong rationale for combining HT with chemotherapy (CT). New chemotherapeutic agents, such as irinotecan, oxaliplatin, gemcitabine and taxane, have been demonstrated to show thermal enhancement in several *in vitro* and/or *in vivo* studies.

With regional or local HT, drug- and heat-induced toxicity can be localized, and systemic toxicity can be avoided or minimized. Generally, regional HT is less invasive than interstitial or intracavitary local HT, and can enhance chemotherapeutic effects in specific sites in the body. In many instances, systemic CT represents the most useful option for patients with surgically incurable malignant neoplasms. An approach which combines systemic CT with regional HT should be of interest, since it can enhance the efficacy of systemic chemotherapeutic drugs in specific areas. Here, we review clinical results of systemic CT combined with regional HT for the treatment of malignant neoplasms.

Key Words: chemotherapy, hyperthermia, cancer, chemo-sensitizer, regional heating

## Introduction

The rationale for the use of hyperthermia (HT) in the treatment of cancer is based on several mechanisms[1]. HT is known to be directly cytotoxic to cancer cells, and also acts as a radiation-sensitizer and chemo-sensitizer. Although the combination of HT with radiation has been the focus of most attention, there is an equally strong rationale for combining HT with chemotherapy (CT). Moderate or even mild HT enhances the cell killing effects *in vivo* of a number of chemotherapeutic agents, such as cyclophosphamide, melphalan, mitomycin C, cisplatin, carboplatin, doxorubicin, bleomycin and the nitrosoureas. New chemotherapeutic agents, such as docetaxel, paclitaxel, irinotecan, oxaliplatin and gemcitabine, have also produced thermal enhancement in several *in vitro* and/or *in vivo* studies (Table I)[2–14]. Generally, interaction or enhancement is only seen when the two treatments are given in

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**Table I.** Thermal enhancement and timing of drug administration for new chemotherapeutic agents with hyperthermia

| Series | Year | *In vitro* or *in vivo* | Temperature (°C) | Timing of anticancer drug administration of *in vivo* study |
|---|---|---|---|---|
| Irinotecan | | | | |
| Kondo[2] | 1995 | *in vitro* | 44* | — |
| Katschinski[3] | 1999 | *in vitro* | 41.8 | — |
| Mohamed[4] | 2003 | *in vivo* | 41.5 | Immediately before HT |
| Le Page[5] | 2006 | *in vitro* | 39-44 | — |
| Gemcitabine | | | | |
| Haveman[6] | 1995 | *in vitro* | 43 | — |
| Van Bree[7] | 1999 | *in vivo* | 43 | 48 h before HT |
| Mohamed[4] | 2003 | *in vivo* | 41.5 | Immediately before HT |
| Vertrees[8] | 2005 | *in vivo* | 40 | 24 h after HT |
| Oxaliplatin | | | | |
| Rietbroek[9] | 1997 | *in vitro* | 41, 43 | — |
| Urano[10] | 2002 | *in vitro* | 38-44.5 | — |
| Mohamed[4] | 2003 | *in vivo* | 41.5** | Immediately before HT |
| Atallah[11] | 2004 | *in vitro* | 42 | — |
| Paclitaxel | | | | |
| Sharma[12] | 1998 | *in vivo* | 43 | Immediately before HT |
| Cividalli[13] | 2000 | *in vivo* | 43 | Various*** |
| Othman[14] | 2001 | *in vitro* | 43 | — |
| Docetaxel | | | | |
| Mohamed[4] | 2003 | *in vivo* | 41.5 | Immediately before HT |

*at low doses, **at high doses, ***24 h, 4 h, and 15 min before, or 15 min and 4 h after HT
HT : hyperthermia

close sequence. However, the effectiveness of the combination of gemcitabine and HT may be schedule-dependent, because the combination of HT followed by gemcitabine 24 hours later, or the administration of gemcitabine followed by HT 48 hours later was more effective than other temporal combinations in two published experimental studies[7,8]. 5-fluorouracil (5-FU) has been shown to produce thermal enhancement under specific conditions such as with low doses and with continuous infusion protocols[15], although there has been no evidence for more than an a additive effect when a single intraperitoneal administration of 5-FU with simultaneous heating is used[16]. Various mechanisms may account for increased chemotherapeutic effects at elevated temperatures, e.g. increased drug uptake into cells, increased DNA damage, decreased DNA repair, reduced oxygen radical detoxification and increased membrane damage[17]. In addition, experimental reports have shown that the use of HT with many chemotherapeutic drugs has the potential ability to reverse drug resistance, although the mechanisms underlying a reversal of drug resistance are not well defined[18,19].

Clinical trials using HT have been performed using one of the following three heating methods ; (I) whole body HT, (II) regional HT, e.g. pelvic, extremity and specific organs, and (III) local HT, e.g. interstitial and intracavitary local heating. CT-induced systemic toxicity may be the most critical factor to be considered in the clinical application of thermochemotherapy. Such toxicity is likely to be

enhanced when the whole body is heated, and this limits the use of whole body HT[20]. With regional or local HT, drug- and heat-induced toxicities can be localized and systemic toxicity can be avoided or minimized. Generally, regional HT is less invasive than interstitial or intracavitary local HT, and can enhance chemotherapeutic effects in various sites in the body, although the application of regional HT requires more sophisticated planning, thermometry and quality assurance than local heating. In many instances, systemic CT represents the most useful option for patients with surgically incurable malignant neoplasms. Thus, an approach using systemic CT with regional HT should potentially be of much interest, since this approach enhances the efficacy of systemic chemotherapeutic drugs in specific areas. This review will summarize the current status of systemic CT combined with regional HT in the treatment of malignant neoplasms.

### *Soft tissue sarcomas*

Although soft tissue sarcomas represent a heterogeneous group of relatively rare malignancies with a wide spectrum in terms of histological type and prognosis, clinical results of the use of systemic CT with regional HT were reported more frequently for this group than for any other malignant neoplasms (Table II)[21–32]. The use of limb-sparing surgery and adjuvant radiotherapy has become standard practice in the management of resectable soft tissue sarcomas of the extremities[33]. But the anatomical location and invasiveness of soft tissue sarcomas often prevents resection with an adequate margin, and high-grade soft tissue sarcomas present problems in terms of local control and a high frequency of distant

**Table II.** Systemic chemotherapy with or without regional hyperthermia for soft tissue sarcomas

| Series | Year | Tumor characteristics, lines of cemotherapy | Pt. (n) | Chemotherapy | HT (device) | Outcomes |
|---|---|---|---|---|---|---|
| Neoadjuvant therapy for high risk soft tissue sarcoma | | | | | | |
| Pezzi[21] | 1990 | High risk | 46 | ADR-based | None | OR 24%, MST 52 mos. |
| Pisters[22] | 1997 | Stage IIIB | 46 | ADR-based | None | OR 28%, 5y-OS : 59% |
| Gortzak[23] | 2001 | High risk | 67 | IFO+ADR | None | OR 28%, 5y-OS : 65% |
| Issels[24] | 2001 | High risk | 59 | VP16+IFO+ADR | BSD 2000 | OR 17%, MST 52 mos. |
| EORTC 62961 | | High grade primary, recur. | >150 | VP16+IFO+ADR | BSD 2000 | Ongoing* |
| Unresectable, recurrent or metastatic soft tissue sacoma | | | | | | |
| Le Cesne[25] | 1995 | Advanced, 2nd | 40 | IFO (high-dose) | None | OR 33%, MST 12 mos. |
| Nielsen[26] | 2000 | Advanced, 1st or 2nd | 114 | IFO (high-dose) | None | OR 16%, MST13 mos. |
| Talbot[27] | 2003 | Unresec. or metas., various | 25 | Temozolomide | None | OR 8%, MST 13 mos. |
| D'Adamo[28] | 2005 | Metas., 1st or 2nd | 17 | ADR+bevacizumab | None | OR 12%, MST 16 mos. |
| Von Burton[29] | 2006 | Unresec. or metas., 1st | 46 | GEM | None | OR 7%, MST 6 mos. |
| Bay[30] | 2006 | Unresec. or metas., various | 133 | GEM+TXT | None | OR 18%, MST 12 mos. |
| Issels[31] | 1990 | Recur. after RT, 2nd** | 38 | VP16+IFO | BSD 1000 | OR 26%, MST 8 mos. |
| Fiegl[32] | 2004 | Unresec. or metas, 2nd*** | 12 | IFO+CBDCA+VP16 | BSD 2000 | OR 20%, MST 15 mos. |

*Phase III randomized study

**2nd line chemotherapy in doxorubicin-refractory soft tissue sarcoma

***2nd line chemotehrapy in doxorubicin-isofamide-refractory soft tissue sarcoma

HT : hyperthermia, OR : objective response rate (complete response+partial response), MST : overall median survival time, OS : overall survival rate, ADR : doxorubicin, IFO : ifosfamide, VP16 : etoposide, GEM : gemcitabine, TXT : docetaxel, CBDCA : carboplatin

metastases. Therefore, the role of neo-adjuvant CT is still the subject of investigation. Issels and co-workers[24,31,32] have systematicallly applied regional HT with systemic CT to improve the prognosis of advanced sarcomas ; a protocol using etoposide, doxorubicin and ifosfamide with regional HT as a neo-adjuvant therapy for high-risk soft tissue sarcoma was initiated in 1991[24]. In 59 patients treated, the objective response rate (complete response+partial response) was 17%, and at the time of surgery, complete necrosis had occurred in 6 patients and > 75% necrosis was seen in 12 patients. Nevertheless, the objective response rate in this study was lower than the 24-29% reported for other neo-adjuvant chemotherapeutic treatments[21-23]. This argues for a high burden of patients with unfavorable prognosis in Issel's study, in contrast to other protocols where only patients were included who were judged to have resectable tumors before the start of neo-adjuvant CT[34]. On the basis of Issels's study, the European Organization for Research on the Treatment of Cancer (EORTC) is conducting additional testing as a first-line treatment, the use of systemic CT with or without regional HT for high-risk soft tissue sarcomas in a multicenter prospective phase III trial[34].

Clinical management of patients with unresectable, recurrent or metastatic soft tissue sarcomas remains a challenging problem and is even more challenging when a disease refractory to first-line CT arises in these patients. The objective response rate to recent protocols which involved gemcitabine, docetaxel, temozolomide or bevacizumab for unresectable or recurrent soft tissue sarcomas was only 7-18%[27-30]. As previously promising results suggested, high-dose ifosfamide treatment for advanced soft tissue sarcomas showed objective response rates of 16-30%[25,26]. However, this regimen caused substantial toxicity such as grade 3 and 4 haematological toxicities in 78-100% of the patients, and non-haematological toxicities in 30-39%. In this context, Issels *et al.* reported on a phase II study of systemic CT with regional HT in 38 patients with locally advanced sarcomas who had relapsed after prior surgery and radiotherapy, and had not responded to previously when given CT alone[31]. HT was combined with etoposide and ifosfamide ; etoposide was given prior to HT, while ifosfamide was infused during the regional HT. The objective response rate was 26% and the most effectively heated tumors showed the highest response rate. In addition, a potential ability to reverse drug resistance was recognized, because some patients previously treated with ifosfamide achieved local tumor control. Fiegl *et al.* examined the efficacy and safety of ifosfamide, carboplatin and etoposide as second-line regimens in combination with regional HT[32]. The objective response rate was 20% and the median survival was 14.6 months. With regards to toxicity concerns, serious regional HT-related toxicity effects or increases in CT-related side-effects were not observed in these studies. These results revealed that systemic CT combined with regional HT showed higher response rates than recent CT protocols alone for unresectable or recurrent soft tissue sarcomas, and was similarly effective when compared to high-dose ifosfamide treatment. Due to limited therapeutic options in treating refractory and advanced soft tissue sarcomas, systemic CT with regional HT should be considered as an alternative treatment.

***Head and neck cancers***

There are three randomized phase III trials using radiotherapy with or without HT for advanced head and neck cancers[35-37]. Two of the three trials showed improvements in the local control rates, and one also revealed a significant increase in the survival rate[35,36].

Only two papers reported the use of CT with HT for head and neck cancers, and the results were encouraging (Table III). In 1979, Arcangeli *et al.* reported that the results of using low doses of adriamycin or bleomycin combined with HT on 7 patients with multiple neck node metastases from head

**Table III.** Systemic chemotherapy with regional hyperthermia for malignant neoplasms except for soft tissue sarcomas

| Series, year | Year | Tumor characteristics | Pt. (n) | Chemotherapy | Hyperthermia device | Outcomes |
|---|---|---|---|---|---|---|
| Head and neck cancer | | | | | | |
| Arcangeli[38] | 1979 | Multiple LN metas. | 15 | ADR or BLM | UHF* | OR 100% |
| Pilepich[39] | 1989 | Recur. after RT | 12 | BLM | MW**, US*** | OR 83% |
| Lung cancer | | | | | | |
| Matsuda[45] | 1993 | Advanced | 14 | CDDP±VDS | RF-8 | OR 21% |
| Ohguri[46] | 2006 | Stage IV, recur. | 14 | TXL+CBDCA | RF-8 | OR 57% |
| Breast cancer | | | | | | |
| Park[53] | 2001 | Recur. after RT | 23 | Doxil | Planar array**** | OR 57% |
| Zoul[50] | 2004 | Recur. after RT | 7 | TXL | Sonotherm 1000 | OR 100% |
| Gastric cancer | | | | | | |
| Kakehi[55] | 1990 | Stage IV, mostly | 33 | MMC+5FU | RF-8 | OR 39% |
| Pancreatic cancer | | | | | | |
| Falk[57] | 1986 | Resec., unresec. | 77 | MMC+5FU±IM | 13.5MHz***** | 1y-OS 27% |
| Kakehi[55] | 1990 | Stage III, IV | 22 | MMC+5FU | RF-8 | OR 36% |
| Ohno[58] | 1993 | Unresec., recur. | 11 | MMC+5FU | BSD 1000 | MST 6 mos. |
| Miyazaki[60] | 2004 | Unresec., metas. | 10 | GEM | Thermox 500 | MST 7 mos. |
| Cervical cancer | | | | | | |
| Rietbroek[65] | 1997 | Recur. after RT | 23 | CDDP | 70MHz****** | OR 52% |
| de Wit[66] | 1999 | Recur. after RT | 19 | CDDP | BSD 2000 | OR 53% |
| Prostate cancer | | | | | | |
| Ueda[68] | 2006 | Stage D2 | 15 | CDDP | RF-8 | OR 46% |
| Colorectal cancer | | | | | | |
| Ohno[58] | 1993 | Unresec., recur. | 12 | MMC+5FU | BSD 1000 | OR 33% |
| Hager[69] | 1999 | Liver metas. | 30 | 5FU/LV+MMC | EHY-2000 | MST 11 mos. |
| Hildebrandt[70] | 2004 | Recur.after RT | 8 | L-OHP+5FU/LV | BSD 2000 | OR 25% |
| Narisada[71] | 2006 | Metas. | 15 | L-OHP+5FU/LV | RF-8 | OR 73% |
| Ohguri[46] | 2006 | Metas. | 12 | CPT-11±5FU | RF-8 | OR 33% |
| Bladder cancer | | | | | | |
| Kakehi[55] | 1990 | NA | 8 | M-VAC etc. | RF-8 | OR 75% |
| Rietbroek[73] | 1996 | Recur. after RT | 4 | CDDP | 70MHz****** | OR 50% |
| Ovarian cancer | | | | | | |
| Secord[74] | 2005 | Recur. | 30 | Doxil | BSD-Sigma 60 | OR 10% |

*Ultra high-frequency wave apparatus
**915MHz microwave device
***1MHz ultrasound device
****16-element planar array microwave or ultrasound applicators
*****13.5MHz capacitive radiofrequency device
******70 MHz four antenna phased array system
OR : objective response rate (complete response + partial response), MST : overall median survival time, OS : overall survival rate, ADR : doxorubicin, BLM : bleomycin, CDDP : cisplatin, VDS : vindesin, Doxil : lposomal doxorubicin , TXL : paclitaxel, CBDCA : carboplatin, MMC : Mitomycin C, 5FU : 5-fluorouracil , IM : immune stimulation, GEM : gemcitabine, LV : folnic acid, L-OHP : oxaliplatin, CPT-11 : irinotecan, M-VAC : methotrexate vinblastine doxorubicin and cisplatin, NA : not available

and neck cancers[38] and all the patients showed objective responses (3 complete responses and 4 partial responses). Pilepich *et al.* also described the results of using the same regimen on 12 patients with persistent or recurrent tumors in the head and neck area after a full dose definitive radiotherapy, in which 4 complete responses and 6 partial responses were reported[39].

***Lung cancer***

Promising results of radiotherapy plus regional HT using RF-8 have been reported for the treatment of lung cancer by Japanese investigators[40-42]. In addition, several reports showed the usefulness of perioperative intrathoracic administration of chemotherapeutic agents plus HT for malignant pleural dissemination and effusion from lung cancer or malignant mesothelioma[43,44].

Reported results using systemic CT with HT in lung cancer are rare[45,46]. In 1993, Matsuda *et al.* reported a multi-institutional analysis of cisplatin-based CT plus regional HT in patients with advanced lung cancer, who could not achieve local control using CT alone ; an objective response was achieved in 3 (21%) of 14 patients[45]. Combination of paclitaxel and carboplatin has been a widely used chemotherapeutic regimen for NSCLC in the USA, because of its low toxicity profile and efficacy[47]. Preliminary results have been reported using systemic CT with paclitaxel and carboplatin plus regional HT for stage IV or recurrent non-small cell lung cancer[46]. The median time to progression of disease was 6 months and the objective response rate was 57% which was higher than the major results of 21-44% with CT alone using paclitaxel and carboplatin for stage IV non-small cell lung cancers[48].

***Breast cancer***

The efficacy of radiotherapy plus HT in locally recurrent breast cancer was demonstrated in several studies, and confirmed by meta-analysis of 5 randomized clinical trials[49]. In the meta-analysis, the complete response rate for radiotherapy alone was 41% while for the combined treatment, it was 59%.

There are some reports on the use of chemotherapy plus HT for breast cancer. The combination of systemic CT using paclitaxel with HT for locally recurrent breast cancer was used by Zoul *et al.* and an objective response was observed in all treated patients[50]. Since the objective response rate of paclitaxel in monotherapy for metastatic breast cancer is in the range of 20-60%, this regimen seems to be effective[51].

Drug-containing liposomes combined with HT have been shown to increase both liposomal delivery and drug extravasation into tumor xenografts[52]. A phase I/II trial was performed in patients with chest wall recurrence of breast cancer using superficial HT immediately before administration of doxorubicin-containing liposomes (Doxil)[53]. The objective response rate in the heated fields was 57%, and the response in heated lesions was significantly higher than that in non-heated lesions. In addition, Kouloulias *et al.* reported a phase I/II study of liposomal doxorubicin in combination with re-irradiation and HT for recurrent breast cancer. Tumor response was demonstrated in all patients accompanied with a good tolerance[54].

***Gastric and pancreatic cancers***

In studies of the treatment of gastric cancer, regional HT in combination with systemic CT using mitomycin C and 5-FU was reported in Japanese multi-institutional clinical studies[55]. An objective

response was achieved in 11 (33%) of 33 patients with gastric cancer (29 at stage IV, and 4 at stage II). This regimen also showed an objective response in 36% of the patients with stage III or IV pancreatic cancer. Although perioperative peritoneal hyperthermic CT using cisplatin and mitomycin C for advanced gastric cancer with peritoneal carcinomatosis has demonstrated a better control of disseminated lesions[56], the clinical results of systemic CT using cisplatin, S-1, irinotecan and taxane, which have been a common regimen in gastric cancer for several years, in combination with regional HT, have not yet been reported.

Gemcitabine monotherapy is considered to be the standard treatment for inoperable and/or metastatic pancreatic cancers, improving overall survival and performance status, maintaining body weight, and reducing analgesic consumption ; however, the objective response rate still remains low[59]. Recently, Miyazaki *et al.* reported on clinical results using low doses of gemcitabine (200mg/body) with regional HT in 10 patients with unresectable or metastatic pancreatic cancers, and observed a median survival time of 7 months without grade 3 or 4 toxicity[60]. Further investigation of this combination therapy including conventional doses of gemcitabine is needed, since major results with conventional doses of gemcitabine (1,000mg/m$^2$) alone for advanced pancreatic cancer is poor ; the median survival time is only 5 to 6 months[59,61].

***Pelvic tumors***

The 'Dutch Deep Hyperthermia Group' in 2000 published the most important study on the role of regional HT in patients with pelvic tumors[62]. It showed improvement of local efficacy in a mixed cohort of patients with locally advanced cervical, bladder or rectal carcinoma, and a major survival benefit was obtained in patients with cervical cancer by adding regional HT to radiotherapy. In addition, phase II studies suggested that clinical results for cervical cancer may be further improved when CT is added to radiotherapy and HT[63,64]. Several studies of systemic CT plus regional HT without radiotherapy for pelvic tumors were also reported[65,66].

A phase II trial combining cisplatin with regional HT was initiated by Rietbroek *et al.*[65]. Twenty-three patients with previously irradiated and recurrent cervical cancer received weekly cisplatin with regional HT. The objective response rate was 52%, with a median duration of response of 9.5 months and a 1-year survival rate of 42%. De Wit *et al.* described a similar approach in 19 patients with previously irradiated recurrent cervical carcinomas and the objective response rate was 53%[66]. These two studies showed that this combined therapy for previously irradiated and recurrent cervical carcinoma is an attractive regimen, because the objective response rate with cisplatin alone in patients with a pelvic recurrence after radiotherapy is low with upper limits of only 15% in most studies[67]. For prostate cancer at stage D2, the combination of cisplatin and regional HT also reveals a favorable response rate of 46%[68].

Hildebrandt *et al.* reported a pilot study of regional HT as an adjunct to systemic CT with oxaliplatin, folnic acid and 5-FU in pre-irradiated patients with locally recurrent rectal cancer[70]. This regimen was feasible on an outpatient basis, and 2 of 8 patients achieved an objective response. Narisada *et al.* also showed favorable preliminary results of a combined treatment of oxaliplatin, folnic acid and 5-FU with regional HT and hyperbaric oxygen treatment for metastatic colorectal cancer[71]. At

the same time, Ohguri *et al.* reported preliminary results of using irinotecan plus regional HT for metastatic colorectal cancer[46].

For bladder cancer, clinical data for systemic CT with HT are limited. The efficacy of local HT combined with intravesical CT for superficial bladder cancer has been demonstrated by Colombo and co-workers[72]. Rietbroek *et al.* used weekly cisplatin and regional HT treatments for locally advanced bladder cancers, and an objective response was observed in 2 of 4 patients[73]. In Japanese multi-institutional clinical studies, 8 patients with bladder cancer were treated with systemic CT using various chemotherapeutic drugs and regional HT, and an objective response was observed in 6 of 8 patients[55].

Recently, a phase I/II study of doxorubicin-containing liposomes combined with regional HT was conducted by Secord *et al.* in patients with recurrent and persistent ovarian cancer[74]. Although this regimen showed a possible improvement in the quality of life, the clinical trial did not demonstrate an increased efficacy when compared with prior reports using doxorubicin-containing liposomes alone, partly because all the patients in this study had been heavily pre-treated and platinum/taxane-resistant.

***Toxicities***

Randomized phase III studies with regional HT did not show any increases in acute or late toxicity from radiotherapy[75]. The pilot studies and phase II trials of systemic CT with regional HT as mentioned above also demonstrated that HT did not adversely impact the tolerability of chemotherapeutic drugs, even when given at maximum tolerated single modality doses[24,66].

Regional HT-related toxicity, such as reversible pain, skin burns and subcutaneous fatty necrosis, was observed in a small proportion ($< 20\%$) of patients, but generally, these healed spontaneously and did not result in discontinuation of the treatment[76]. Exceptionally, Issels *et al.* observed two cases of severe subcutaneous fat/muscle necrosis which required surgical intervention and interruption of the regional HT-combined chemotherapy cycles[31].

Experimental studies have demonstrated the radiosensitizing effect of HT on spinal cord damage and direct damage to the spinal cord from HT alone[77]. From clinical experiences with whole body HT and hyperthermic isolated limb perfusion combined with CT, the occurrence of neuropathies is well known ; however, with regional HT, the incidence of even mild neurological complications is very low[78].

## Closing comments

Clinical experience with a combination of systemic CT and regional HT is limited, but current results are promising, especially for recurrent tumors after radiotherapy, and for tumors with chemotherapeutic drug-resistance.

The effect of regional HT depends strongly on the heating technique, since, with current devices, the radiofrequency-output must be used at maximum possible levels, and at the maximum levels tolerated by patients in order to elevate tumor temperatures to therapeutic levels. The use of more advanced HT machines, and proper location and levels of heat delivery are required, and a well-trained staff is essential for the use of this type of therapy.

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## Abstract in Japanese

# 領域加温によるハイパーサーミアを併用した全身化学療法

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**要　　旨**：温熱化学療法が理想的な併用療法であるとする十分な基礎的根拠が，温熱放射線治療の場合と同様に認められる．イリノテカン，ジェムシタビン，オキサリプラチンやタキサンといった新規抗癌剤においても，温熱による増感が認められている．しかし，その臨床的有用性に関する検討は温熱放射線治療と比べ乏しい．領域加温では加温による抗癌剤の毒性増強は全身加温に比べて限局しており，その毒性を回避又は最小限に抑えることが可能である．また，組織内加温や腔内加温と比べ浸襲性が低く，加温領域設定時の自由度が高い．全身化学療法は，根治手術が不可能な悪性腫瘍に対して，一般に用いられる治療法である．領域加温との併用によって，全身に投与された抗癌剤の増感を加温領域という特定領域において期待する事ができ，大いに注目すべき治療法と思われる．ここでは全身化学療法と領域加温によるハイパーサーミアの併用の臨床成績を概説する．