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1．招へい責任者 平岡 真寛 ㊞

所属機関 京都大学大学院医学研究科放射線医学講座 職名 教授

所在地 〒606-8507 京都市左京区聖護院川原町54 電話 (075) 751-3417

招へい研究者氏名 朱 京麗

所属機関 北京中日友好病院 放射線腫瘍科 職名 副主任医師

研究テーマ 難治癌に対する各種先端的放射線治療法の臨床的研究

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および、医学部附属病院放射線科において、

各種先端的放射線治療法の情報交換

あるいは技術習得を行った。

3．研究報告

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研究テーマ

難治療に対する各種先端的放射線治療法の臨床的研究

来日研究者氏名

朱　京麗

中国での所属・役職

北京中日友好病院放射線腫瘍科　　副主任医師

招聘者氏名

平岡　真寛

所属・役職

京都大学大学院医学研究科放射線医学講座　教授

（要旨）

原発性、転移性骨腫瘍に対する局所温熱療法の評価

１９８２年から１９９７年までに京都大学で温熱療法を行った原発性、転移性骨腫瘍症例を検討した。治療を行ったのは、合計１６人の１９部位で局所温熱療法を中心として放射線療法や化学療法との併用効果を評価した。これらの患者に対して、のべ８６回の治療を行い、その内５５回で効果腫瘍内温度測定を行った。腫瘍内最高、平均、最低温度は、各々42.9,40.4,41.6℃であった。１２腫瘍（６３％）で腫瘍内最高温度は42.5℃をこえた。CT画像で評価した局所腫瘍制御は、15.8%でみられた。また局所疼痛制御は62.5%であった。１年累積生存率は60%であった。我々の初期臨床研究は、原発性および転移性骨腫瘍に対する温熱療法の有用性を証明するものである。

Preliminary clinical results of locoregional hyperthermia for primary and secondary bone tumors

(ABSTRACT)

Nineteen primary and secondary bone tumors in 16 patients were treated with hyperthermia plus radiotherapy and/or chemotherapy between 1982 and 1997 at Kyoto University Hospital. The thermometric and clinical results were analyzed retrospectively. In 55 of 86 hyperthermia sessions, the intratumor temperature was measured using a thermometer. Of the 19 tumors, 16(84%) received heat treatment 4-7 times, and 3(15.8%) received 1or 2 treatments of hyperthermia. The mean maximum, mean minimum and average intratumor temperatures were 42.9, 40.4 and 41.6℃, respectively, and 12(63%) reached a tumor maximum temperature above 42.5℃. The durations that intratumor points exceeded 42, 41 and 40℃ were 27, 33.8 and 37.9 minutes, respectively. The local tumor response to treatment was assessed using X-ray computed tomography. The local response rate was 15.8% and the local pain relief rate was 63.2%. The 1-year cumulative survival rate was 60%. Our preliminary results indicated that thermoradiotherapy and thermochemotherapy are clinicaly feasible and potentially beneficial in the management of locally advanced bone tumors.

Keywords: Bone tumor, Hyperthermia, Radiotherapy, Chemotherapy, Thermometry

1. Introduction

Locally advanced or recurrent primary and metastatic bone tumors are considered to be refractory to conventional treatment modalities. Patients with bulky bone tumors often complain of intractable pain. In such patients, surgical treatment is seldom an option, and the efficacy of conventional radiotherapy and chemotherapy remain unsatisfactory. Hyperthermia in combination with radiotherapy and/or chemotherapy is expected to be effective for these tumors.

During the past 2 decades, hyperthermia in combination with radiotherapy or chemotherapy has been investigated basically and clinically as a new cancer treatment modality (Abe and Hiraoka 1990). In our department, hyperthermia has been employed for the treatment of locally advanced or recurrent primary and metastatic bone tumors since 1982. We herein retrospectively analyzed the thermometric and clinical results of this treatment to determine whether or not the temperature of bone tumors could be elevated to the therapeutic range of hyperthermia, and whether hyperthermia in combination with radiotherapy and/or chemotherapy improves the local control, quality of life and survival. In addition, the toxicity of the treatment was examined.

2. Materials and Methods

2.1 Patients

Nineteen primary and metastatic bone tumors in 16 patients underwent

hyperthermia from August 1982 to June 1997. The patients consisted of 11 males and 5 females and their ages ranged from 14 to 76 years with a mean of 58 years. All patients complained of pain.

All patients had histologically confirmed malignant tumors. Of the 19 tumors,10 were primary tumors in 8 patients which consisted of 4 osteosarcoma, 3 chordoma, 2 chondrosarcoma, and 1 Ewing's sarcoma: The remaining 9 tumors in 8 patients were metastatic bone tumors and the primary sites were the liver in 4, the thyroid in 2, the kidney in 1, the urinary bladder in 1 and the colon in 1. The tumor volume was calculated by the formula $\pi abc/6$ and it ranged from 65.4 to 1565cm^3 with a mean of 539 cm^3. Treatment sites were the pelvis in 16 , chest wall in 2 and lower extremity in 1.

Prior treatment consisted of systemic chemotherapy in 3 tumors, transcatheter arterial embolization (TAE) and transcatheter arterial infusion (TAI) in 5, radiotherapy in 5, hyperthermia in 3 and surgery in 3. Five of the 19 tumors received a multimodality approach and 7 received a single modality approach. The remaining tumors were not pretreated in the treatment site.

2.2 Hyperthermia

Three types of heating equipment were used for locoregional hyperthermia depending on the tumor volume, anatomic location and depth from surface. The methods of heating treatment and temperature

measurement were described previously (Hiraoka et al. 1994, Mitsumori et al.1996, Nishimura et al. 1990). In brief, an 8 MHz radiofrequency (RF) capacitive heating device(Thermotron RF8, Yamamoto Vinita Co., Osaka, Japan) was employed for treating 15 deep-seated or large subsurface tumors. In general, 2 opposing electrodes were used and the sizes of the pair of electrodes were determined according to the size and location of the tumors. When the tumor was located at the central part of the anatomical site, a pair of same-sized electrodes was used. Otherwise, a pair of different-sized electrodes was employed to shift the high temperature area to the tumor side.

Three heating treatments were employed using an ultrasound heating system (Shimadzu Corporation, Kyoto, Japan). This device had an improved center holed planar transducer, which minimized the hot spots at the central axis and provided homogeneous distribution of acoustic fields. The frequency and diameter of the applicator was selected, according to the size and depth of the tumor. A single heating treatment was performed using a 430 MHz microwave heating apparatus with a lens applicator (HTS-100, Tokyo keiki Co. Ltd., Tokyo, Japan), for a subsurface tumor.

A temperature-controlled water pad or water circulation unit was used in all heat treatments, to control the temperature of the skin surface and subcutaneouslayer. Hyperthermia was delivered for 30-65 minutes (mean, 43.4 min.), once or twice weekly, within 30 minutes following

radiotherapy. The power was increased in a stepwise manner until the intratumor temperature reached the therapeutic range or the patient became tolerate the treatment.

Sixteen of the 19 tumors received heating treatment 4-7 times. The remaining 3 tumors received the treatment only 1 or 2 times, partly due to intolerance of sufficient power elevation, and partly due to a poor general condition.

The blood pressure, pulse rate and body temperature were measured before, during and after heating treatment.

2.3 Tumor Temperature Measurement

The intratumoral temperature was measured using a thin Teflon-coated microthermocouple probe. The probe was inserted into the tumor via a 21-gauge angiocatheter that had been introduced into the deepest part of the tumor with the aid of ultrasonic guidance or X-ray computed tomography (CT). The thermal distribution within the tumor was obtained either by withdrawing the thermocouple by 1 cm step during and immediately after hyperthermia with a single point thermocouple, or by using a stationary multipoint thermocouple probe.

We defined Tmax., Tmin., and Tave. as the maximum, minimum and average intratumoral temperature in a thermal distribution recorded at the termination of treatment, respectively. In addition, T>42℃, T>41℃ and T>40℃ were defined as the duration that intratumor point exceeded 42℃, 41

℃, and 40℃, respectively.

2.4 Combination Therapy

Hyperthermia was combined with radiotherapy and/or chemotherapy. Radiotherapy was applied using megavoltage photons of 6 and 15 MV or 60 Co for 15 of the 19 tumors. The prescribed dose and fractionation was 37.0-61.2 Gy in 1.8-2.5 Gy per fraction for 12 tumors, and 27.0-32.0 Gy in 3-4 Gy per fraction for 3 other tumors, 5 times weekly, respectively.

Hyperthermia was administered after radiotherapy, usually within 30 minutes. In 4 of the 15 tumors, both radiotherapy and TAE and/or TAI were combined with hyperthermia. The anti-cancer drugs used were cisplatin and doxorubicin. One of the 19 tumors was given concurrent systemic chemotherapy using cisplatin 50mg /㎡, weekly, for 4 cycles, intravenously. Three of the 19 tumors were treated by hyperthermia alone, because the tumor had been heavily pretreated. One patient underwent intraoperative radiotherapy after treatment with external radiotherapy in combination with hyperthermia. This tumor was previously considered unresectable.

2.5 Assessment of Response

The local effect to treatment was evaluated by the change in tumor volume (using CT) when the tumor showed maximum regression. CR(complete response) was defined as 100% tumor regression, PR(partial response) indicated more than 50% tumor regression, NC(no change) less than 50% tumor regression and less than 50% tumor progression,

PD(progressive disease) signified more than 50% tumor progression.

Pain control by treatment was evaluated according to the change in pain score before and after treatment. Pain was scored based on multiplied pain severity (0=none, 1=mild, 2=moderate, 3=severe) and pain frequency (0=no pain, 1=occasional, 2=intermittent, 3=constant), with values ranging from 0-9. Complete pain relief (CPR) was defined as a pain score decreasing to zero. Partial pain relief (PPR) represented a pain score below the initial score. Other patients were classified as no pain relief.

The follow-up period ranged from 2 to 95 months. Survival rates were calculated using the Kaplan-Meier method.

3. Results

3.1 Thermometry

Eighty-six hyperthermia sessions were performed for the 19 tumors, and the thermometry was performed in 55 of the 86 (64 %) heat sessions. Intratumoral thermometry was performed in all patients at least 1 time except for 1 patient who refused it.

Table1. shows the thermometry data obtained during heating treatment. The range and average for T>42℃, T>41℃, and T>40℃ were 0-54 minutes (Ave.=27),13-54 minutes (Ave.=33.8) and 15-57 minutes (Ave.=37.9), respectively. The heating time ranged from 36 to 58 minutes (Ave.= 47.3).

The average±SD (standard deviation) values for Tmax., Tmin., and Tave. were 42.9±2.16℃, 40.4±1.43℃ and 41.6±1.27℃, respectively, (Table 2).

Twelve of the 19 tumors reached a maximum temperature of ≧42.5℃. Five out of the19 reached a minimum temperature of >41℃, and 11 out of the19 showed an average temperature of >41℃.

3.2 Local Response and Pain Control Rate

With regards to local response, 3 achieved PR and the remaining 16 showed NC (Table 3) of the 19 tumors treated. The local response rate was 3/19 (15.8%). The local response rate was 3/12 (25%) in 12 tumors in which the intratumoral temperature was ≧42.5℃. A local response was not obtained for tumors with Tmax. below 42.5℃.

Six of the 19 tumors achieved complete pain relief (CPR) and 6 achieved partial pain relief (PPR). A total pain control rate was 12/19 (63.2%). Pain scores before and after the treatment are listed in Table 4. In 9 of 12 tumors in which Tmax. ≧42.5℃, the pain control rate was 9/12 (75 %). On the other hand, in 3 of 7 tumors in which Tmax. <42.5℃, the pain control rate was 3/7 (42.8 %).

Among the 10 primary tumors, 2 obtained PR and 7(70%) reached Tmax. ≧42.5℃. Of the 9 metastatic tumors, 1 achieved PR and 5(55%) reached Tmax. ≧42.5℃.Concerning pain control CPR+PPR, the results were similar for both primary and metastatic tumors.

Figure 1 shows a patient with chordoma who obtained PR and CPR following thermoradiotherapy.

3.3 Survival

The cumulative survival rate of 16 patients is shown in Figure 2. The 1 year and 3 year survival rates were 60% and 25%, respectively. The survival outcome for the 3 partial local responders was 44+in 1 case and 39+ months in another case. The remaining outcome was 59+ months and the patient continues to live with stable disease. The mean survival period of patients with pain relief was 26.8 months. There was no significant difference in survival between primary and seconary bone tumors.

3.4 Toxicity

Regarding blood pressure, the systolic blood pressures before and after heating treatment were 128.8±23.7 mmHg (mean±SD) and 130.6±22.9 mmHg (mean±SD), respectively. The diastolic blood pressures before and after heating treatment were 75.6±13.4 mmHg (mean±SD) and 77.8±15.8 mmHg (mean± SD), respectively. The blood pressure increased in 50 % of the patients, while it decreased in the other 50%.

The pulse rate was elevated in most patients, with a range of 6-51 beats/min. (mean±SD, 18.8±11.7).

The sequelae of hyperthermia were not severe. The majority of the patients reported mild pain associated with heating. The pain disappeared spontaneously after hyperthermia finished. Two patients could not tolerate treatment because of pain, and the treatment was unsatisfactory. Numbness and edema in the treatment regions were observed in 4 and 1 patient,

respectively. There was no thermometry-catheter related complication. No late sequelae were observed in any patient.

4. Discussion

Hyperthermia has been used effectively as an adjuvant to radiotherapy and/or chemotherapy in the treatment of soft tissue tumors (Leopold et al. 1989, Hiraoka et al. 1995), head and neck tumors (Valdagni et al. 1994, Wust et al. 1996), breast cancer (Bornstein et al. 1992), liver tumors (Nagata et al. 1995) and pelvic tumors (Sapozink et al. 1984, Nishimura et al. 1992). To the best of our knowledge, few studies have examined the treatment of bone tumors with hyperthermia. Our results demonstrated that adding hyperthermia to radiotherapy and/or chemotherapy was advantageous without increased side effects in a group of patients with locally advanced primary or metastatic bone tumors.

The thermal parameters showed that hyperthermia for bone tumors is clinically feasible, because the intratumor temperature was heated to a therapeutic temperature. Twelve out of the 19(63%) tumors reached Tmax. ≧42.5℃. Ten out of 19(52%) tumors achieved a Tmax. >43℃. Moreover, 84%(16/19) tumors were treated 4 to 7 times and these patients tolerated the treatment. The thermometric results reported by Matsui et al. (1989) were also positive. According to their study, temperatures above 42.5℃ were observed in the center and surface of pig femurs. Futhermore, the majority of malignant bone tumors was raised to a maximum temperature

above 42.5℃ in a pilot clinical study.

Our findings suggested the following benefits of hyperthermia in the management of locally advanced bone tumors.

The first is that the local control rate may be improved if tumors are heated above 42.5 ℃. The local control rate was 25% (3/12). Since all of these tumors were regarded as refractory to radiotherapy or chemotherapy alone because of their volume, histological type and history of prior therapy, this response was good. The second benefit to patients is pain reduction. Reduced pain was observed even in patients who showed no tumor regression. Twelve out of the19 tumors(63.2%) achieved pain control. A higher pain control rate (75%) was noted in tumors heated above 42.5℃ in the Tmax. than in tumors heated below 42.5℃ whose pain control rate was 42.8% ($p>0.1$). All tumors which achieved either local response or pain relief were heated more than 4 times, except 1, which was heated 2 times. No significant relationship between Tmax. over 42.5℃ and local response or pain relief was found, because the patient number was small. However, the clinical results suggested that Tmax. over 42.5℃ and more than 4 times heat treatments are necessary to obtain local control or pain relief.

The addition of hyperthermia to radiotherapy and/or chemotherapy did not increase the acute complications. Hyperthermia-related toxicity such as subcutaneous fat necrosis and skin burn was not observed.

With regard to the systemic effects of hyperthermia, the pulse rates increased after hyperthermia in all patients, while the blood pressure changed individually.

More recently, a patient's quality of life has become a new criterion for assessing cancer therapy. Our multimodality approach using hyperthermia provided pain relief and tumor volume reduction, suggesting that this treatment method is clinically useful.

In conclusion, our thermometric and clinical results indicate that locoregional hyperthermia is feasible for locally advanced bone tumors. The clinical benefit of hyperthermia in combination with radiotherapy and/or chemotherapy was suggested. Since the number of patients was small, further hyperthermia clinical trials should be performed to confirm these observations.

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