Hyperthermia in Combination with Radiation Therapy for Treatment of Advanced Inoperable Breast Cancer

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Abstract

Twelve breast cancer patients with locally advanced inoperable lesions were studied. Six cases had received chemotherapy, 6 had not. Most of the tumors were ulcerative lesions with an average size of 11.5 cm. The patients were treated with 43°C hyperthermia once or twice a week together with radiation at a dose of 20-70 Gy. Six of them were also treated with concurrent chemotherapy. Two cases responded completely (17%) and 10 cases responded partially (83%). The result indicates that the combination of hyperthermia and radiation, with or without chemotherapy, might be a good treatment option for locally advanced inoperable breast cancer, especially for patients who have had failure or contraindication to chemotherapy. It is an effective treatment for palliation of local symptoms, showing a tendency to achieve local control of large, ulcerative advanced breast lesions especially when such treatment is followed by salvage surgery.

Key word : Breast Cancer, Hyperthermia, Radiation Therapy

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The use of hyperthermia in combination with radiation therapy and chemotherapy has been developed, especially during the past two decades. Hyperthermia can enhance the effect of radiation because, firstly, it has a direct cytotoxic effect which can destroy radioresistant cells especially hypoxic cells and cells that are in the S phase of the cell cycle. Secondly, when combined with radiation, it can also decrease the cell's capability of repairing the sublethal damage inflicted by radiation.

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Breast cancer is one of the most popular areas for using combined treatment because of its superficiality which makes it easy for applying heat and monitoring it. There have been several studies supporting combined radiation and hyperthermia for treatment of chest wall recurrences of breast cancer[1-6] with a thermal enhancement ratio of about 1.5[7-9].

Advanced inoperable breast cancer has only a 6-15 per cent 5-year survival after radiotherapy[4, 5,10]. The local tumor control rate can be improved from 35 to 65 per cent by increasing the radiation dose from 50-60 Gy to 75-100 Gy[11,12]. However, this high radiation dose causes a significant risk of complications to normal tissue, especially the ribs and lung. A combination of hyperthermia and radiation in this group of patients would be beneficial in that it could increase the effect of a modest dose of radiation. Thus, it can provide better local tumor control with a lower risk of complications.

Most chemotherapy has an additive effect when combined with hyperthermia and also has a radiosensitizing effect when combined with radiation. Trimodal therapy of chemotherapy together with hyperthermia and radiation therapy should be beneficial to increase local control and decrease the risk of distant metastases.

The authors started using combined hyperthermia and radiation for breast cancer patients at Siriraj Hospital in 1994 when most of the cases were chest wall recurrences. The objective of treatment was to increase local control. The other group of patients had locally advanced inoperable breast cancer in whom the aim of treatment was palliation of symptoms, such as bleeding and discharge.

MATERIAL AND METHOD

Patients with locally advanced breast cancer treated with hyperthermia in the Radiation Oncology Division Siriraj Hospital were retrospectively reviewed. Inclusion criteria for the study were patients with locally advanced, inoperable breast cancer, patients who had had no previous radiation to the chest and who were being treated with radiation and hyperthermia at Siriraj Hospital. Patients who were lost to follow-up during the course of treatment were excluded from the study.

The radiation therapy machine used was the Cobalt-60 or Linear accelerator with 8-12 MeV electron beams. The fields and radiation doses varied according to the physicians' judgement and the appearance of the tumor.

The equipment and techniques used to maintain hyperthermia were as follows:-

The hyperthermia machine was a Microfocus 1000, (Cheung Laboratories, USA). Heat was generated by a Microwave 915 MHz delivered through 4 antennae external applicators.

Thermometry was performed by optical thermometric probes placed on at least 3 points. One probe pierced the base of the tumor to control the tumor temperature. The other probes were placed on the surface of the tumor and on the skin nearby in order to control the skin temperature.

The temperature was set at 43°C with a feedback mechanism from the sensor within the tumor. The skin nearby was kept under 40°C using an air cooling system, except for cases in which the tumor involved the skin, in these cases the skin temperature was set to 41°C.

Hyperthermia was given once or twice a week for 60 minutes/session.

Concurrent chemotherapy was reviewed and evaluated

Results of the treatment were evaluated after completion of the treatment as follows:- Complete response (CR) described lesions which completely disappeared after treatment. Partial response (PR) described lesion which were reduced in size by more than 50 per cent. No response (NR) described lesions that reduced in size less than 50 per cent and progression of disease (PD) described lesions that progressed despite treatment.

RESULTS

From January 1994 to January 1995, 12 patients with locally advanced, inoperable breast cancer who had never been treated with radiation before were treated with radiation and hyperthermia. The patients' characteristics are shown in Table 1.

Six of them had been previously treated with chemotherapy; 4 out of 6 showed no response, one (patient no. 2) showed a partial response but the tumor was still large and fixed, another one (patient no. 10) had tumor re-growth after being to lost to follow-up with a partial response to chemotherapy. In the group that were chemotherapeutically naive, two elderly patients (patients no. 6,11) had failed to respond to

Table 1. Patient characteristic.

No.	Age (year)	Previous treatment	Response to previous treatment	Tumor diameter prior to RT (cm)	Character of the lesion
1	56	CMF	NR	10	Ulcer
2	71	-	-	8	Ulcer
3	58	CMF	NR	10	Ulcer
4	46	CMF, CAF	NR	10	Ulcer
5	55	-	-	14	Ulcer
6	86	Hormone	NR	15	No skin involvement
7	53	CMF	NR	10	Ulcer
8	43	CMF	PR	4	Ulcer
9	69	-	-	15	Ulcer
10	44	FEC	PR	15	Ulcer
11	82	Hormone	NR	7	Ulcer
12	32	-	-	10	Ulcer

CMF = Cyclophosphamide, Metrotrexate,5-FU, CAF = Cyclophosphamide, Adraimicin, 5-FU, FEC = 5-FU, Epirubicin, Cisplatin, NR = No response, PR = Partial response.

Table 2. Treatment summary for each patient.

No.	RT field	RT Dose (cGy)	TDF	No. of HT	HT schedule	Systemic treatment	Results
1	Local field	6,600	99	6	Once a week	No	CR
2	Local field	2,000	62	5	Once a week	No	PR
3	Wide field	3,300	68	2	Once a week	No	PR
4	Wide field	5,000	82	5	Once a week	No	PR
5	Local field	5,000	82	9	Twice a week	Hormone	PR
6	Wide field	5,000	82	5	Once a week	Hormone	PR
7	Wide field	5,200	86	10	Twice a week	Chemo, Hormone	PR
8	Wide field	5,000	82	2	Once a week	Chemo	PR
9	Wide field	4,400	73	5	Once a week	Chemo *	PR
10	Wide field	5,000	82	4	Once a week	Chemo*	PR
11	Wide field	2,000	66	5	Once a week	Chemo*	PR
12	Wide field	7,000	115	7	Once a week	Chemo*	CR

*Trimodal therapy = chemotherapy, hyperthermia and radiation
HT = Hyperthermia sessions

hormonal therapy and the remaining 4 patients had never received systemic therapy, either due to their medical conditions or refusal of treatment.

The majority of the tumors (11 in 12) were ulcerative masses with a tumor size of 4-15 cm.

Treatment

Among these 12 patients, 8 cases (no. 1-8) were treated by combined radiation and hyperthermia and 4 cases (no. 9-12) were treated by trimodal therapy of concurrent chemotherapy, radiation therapy and hyperthermia.

Radiation technique

The radiation fields and doses are shown in Table 2. Three cases were treated with an involved local field and 8 cases were treated with a wide field (chest wall field). The total tumor dose varied from 20-70 Gy, 2-4 Gy per fraction. The radiation schedule was 5 fractions per week, except in case number 2 who received 4 Gy once a week for 5 weeks.

Hyperthermia

Ten patients received hyperthermia once a week and the other two received hyperthermia twice a week. The number of hyperthermia treatments varied from 2 to 10 treatments with a mean of 5.4 and median of 5 times in total. Details are shown in Table 2.

Chemotherapy

Six patients received a regimen of Cyclophosphamide, Methotrexate and 5-FU (CMF) every

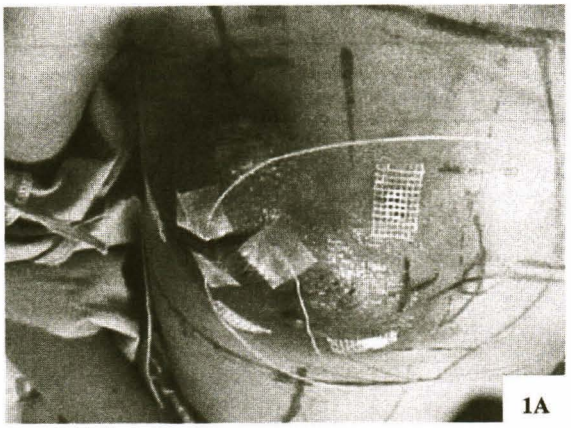

Fig. 1A. **Pre-treatment. A 32 year old patient (patient no. 12) who presented with a 10 cm right breast mass with skin involvement.**

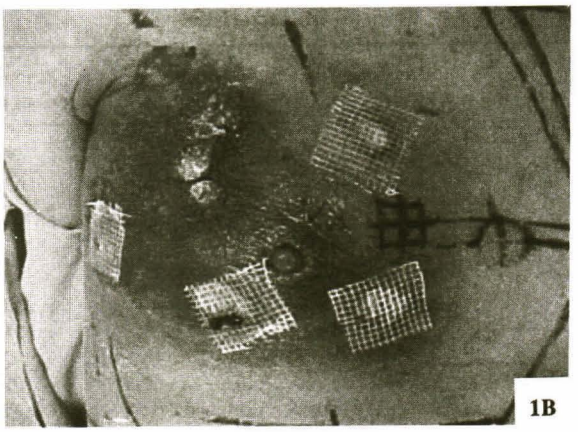

Fig. 1B. **2 weeks after treatment with combined radiation, hyperthermia and chemotherapy, the picture shows significant tumor shrinkage and dryness of the area of skin involved.**

Fig. 1C. **8 months after treatment, the tumor completely disappeared without any severe complications.**

3 weeks or Carboplatin and 5FU (PF) every 4 weeks. There were 3 cases (no. 5-7) who also received hormonal therapy (Tamoxifen or Nolvadex) during the treatment. Four of the patients (no. 9-12) had chemotherapy as part of trimodal therapy by injection or infusion of chemotherapy during hyperthermia treatment.

Of the 8 patients who received only combined radiation and hyperthermia, 7 of them had a partial response (no. 2-8) and the other (no. 1) showed a complete response after radiation (60 Gy, 200 cGy/fraction) and hyperthermia once a week for 6 weeks.

Of the 4 patients who received trimodal therapy, one of them had a complete response (patent no. 12), (Fig. 1A-C) the others had a partial response. The tumors decreased in size and the bleeding and discharge from the tumors also decreased or stopped.

After the treatment, 2 of the 10 patients who had a partial response to combined therapy were sent for toilet mastectomy and acheived local control of the tumor, 2 had further chemotherapy, 2 died from systemic metastases and 2 were lost to follow-up.

There was no severe complication from the treatment, only 2 cases (patients no. 5,7) had moist desquamation of the skin and 1 case (patient no. 3) had progressive arm edema after the treatment.

DISCUSSION

The authors' technique was feasible, and the patients tolerated the treatment well. There were no patients in whom planned hyperthermia sessions were omitted. The treatment with radiation, hyperthermia with or without chemotherapy was completed within the planned time. The skin complication reported seemed to be the result of the hyperthermia radiosensitizing effect. The 2 cases with grade 3 skin complications, 2 months after treatment was completed, the skin lesions had healed. The patient with arm edema

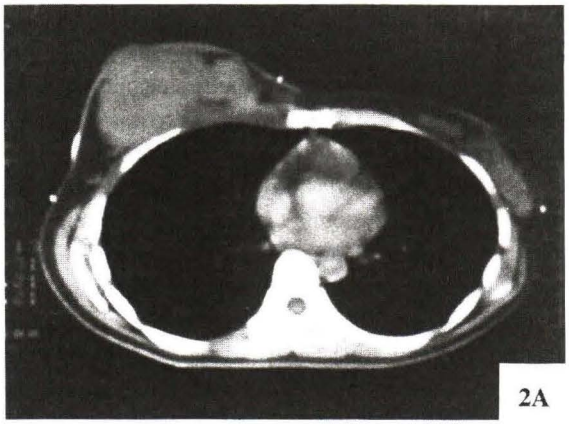

Fig. 2A. Pre-treatment axial CT scan of patient no. 12 showed large right breast mass.

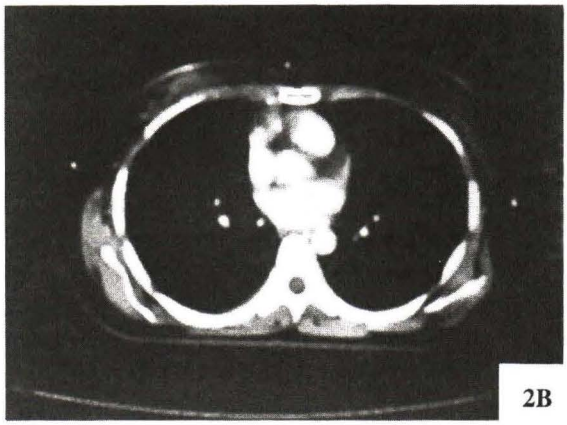

Fig. 2B. Axial CT scan 6 months after treatment, the tumor disappeared without any lung reaction detectable.

(no. 3) had a poor performance status and aggressive disease. The arm edema was the result of a combination of treatment side effect and residual tumor.

The Radiation Therapy Oncology Group (RTOG) recommend 2 catheters cross through midplane and another one at the base of the tumor to measure the tumor dose. However, in the present retrospective study, the authors put only one interstitial catheter at the base of the tumor and 2 others on the surface of the tumor and the skin nearby. This was because the main concern was to give palliative treatment with a minimally invasive procedure in order to help the patient tolerate the treatment well. The measurement taken through these catheters may not represent the actual temperature in all the areas of the tumor which is the main problem for hyperthermia treatment. The authors, however, assumed that the temperature at the base of the tumor would be less than the upper area since the source of heat was applied to the surface of the tumor.

Sapareto[13] reported a method for dealing with variations in temperature and treatment time using 43°C equivalent treatment time "thermal dose (t_{43})". However, in the present retrospective study, the authors could not report the thermal dose in order to compare treatments because this data is unavailable. The treatment time was fixed at 60 minutes and a temperature around 42-43°C was kept for more than 30 minutes for every treatment session.

The other problem the authors ran into was the area treated. The largest hyperthermia applicator used was 7 x 7 cm which is smaller than most of the tumors. Hyperthermia was applied to the ulcerated area most of the time. In cases where the ulcer was very large, the hyperthermic area was divided into 2 areas and heat applied alternately or in some cases, twice a week, one session/area/week.

From the present study, local control of the tumor was achieved in 2 cases using a radiation dose of 60-70 Gy combined with hyperthermia on a weekly basis with concurrent chemotherapy in one case. The number of patients in the present study are too small for statistical analysis of the response to hyperthermia. However, it appeared from these 2 cases with large ulcerative tumors that the tumor size didn't seem to be the main prognostic factor. Patients with a good performance status and younger age responded to curative-intent treatment. These 2 patients received the highest radiation treatment dose (with TDF 99 and 115). This indicates that radiation dose seems to be an important predictor for combined hyperthermia and radiation treatment outcome. Combination with chemotherapy or frequency of hyperthermia (once *vs* twice a week) didn't appear to be the main prognostic factors.

It is interesting that a radiation dose of 60-70 Gy used alone, could rarely achieve local tumor control of an ulcerative tumor 10 cm in size. This

may represent an enhancing effect of hyperthermia when used together with radiation therapy. According to a previous study[12], radiation alone can produce local control of the tumor in 20-50 per cent using a high dose (> 70 Gy). A combination of radiation and hyperthermia can give a higher local control rate[10, 11]. There have been reports using combined radiation and hyperthermia for locally advanced breast cancer[10,11] which showed significantly better results compared to radiotherapy alone (CR 64.3 *vs* 36.4%). These studies reported higher rates of local control of advanced breast cancer than the present study. This could be due to the fact that the tumors in the present study were mostly large and almost all of them (11/12) were ulcerative lesions and were sent to the department for palliative treatment. Li RY et al believe that the optimal size of tumor for combined hyperthermia using microwaves should be less than 5-6 cm in diameter. The aim of combined hyperthermia in the present study was only to provide better quality of life at a late stage. If appropriate cases to be treated with combined modalites were selected, the local control rate should be higher.

Combined chemotherapy used as trimodal-therapy is an effort to improve local control and the response rate of the tumor[14]. The drugs used in the study were Endoxan, Methotrexate, 5FU and Platinum which have supra-additive and additive effects when combined with hyperthermia[7-9] and radiation. Even though there was only one case who achieved tumor control as a result of the trimodal-therapy in the present study, a good response rate and successful palliative treatment of symptoms were noted without any severe complications from the treatment.

As far as we know, breast cancer patients usually die from systemic disease. There are about 10 per cent of breast cancer patients that never showed the effects of systemic metastases even with an aggressive local lesion. This group of patients would benefit from combined treatment and salvage surgery to improve local control and survival. However, the follow-up is too short to be certain and further follow-up is needed.

SUMMARY

A combination of hyperthermia and radiotherapy with or without chemotherapy may be a good option for treatment of advanced, inoperable breast cancer which has failed to respond to chemotherapy alone. The result of combined treatment shows 100 per cent success in palliation of symptoms. Local control of a large ulcerative advanced lesion is possible using combined modalities of treatment, especially when followed by salvage surgery. Trimodal therapy should be considered as the primary treatment for advanced breast cancer in that it will improve local control and decrease the risk of distant metastases.

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การรักษามะเร็งเต้านมระยะลุกลามที่ยังไม่มีการแพร่กระจายโดยการฉายรังสีร่วมกับการรักษาด้วยความร้อน

นันทกานต์ เอี่ยมวนานนทชัย, พบ, พิทยภูมิ ภัทรนุธาพร, พบ*, เยาวลักษณ์ ชาญศิลป์, พบ*, มธุรส สุขเกษม, วทบ**

การศึกษานี้เป็นการศึกษาผลย้อนหลังในผู้ป่วยมะเร็งเต้านมระยะลุกลามขนาดใหญ่ (เฉลี่ย 11.5 ซม) ที่ไม่ตอบสนองต่อการให้ยาเคมีบำบัดหรือผู้ป่วยที่ไม่สามารถให้ยาเคมีบำบัดได้ จำนวน 12 ราย ที่ได้รับการรักษาที่โรงพยาบาลศิริราชในช่วงปี 2537-2538 ด้วยการฉายรังสีปริมาณ 20-70 Gy ร่วมกับการอบความร้อน (Hyperthermia) ด้วยอุณหภูมิ 43° เซลเซียส จำนวน 1-2 ครั้ง/สัปดาห์ ในจำนวนนี้ผู้ป่วย 6 รายได้รับยาเคมีบำบัดร่วมด้วย ผลการรักษาพบว่าก้อนยุบลงเกิน 50% ทั้ง 12 ราย (100%) โดยที่มีผู้ป่วย 2 ราย (17%) ที่ก้อนเนื้องอกยุบหายไปหมดจากการรักษาดังกล่าว นอกจากนี้ผู้ป่วย 2/10 รายที่มีเนื้องอกหลงเหลืออยู่สามารถผ่าตัดเอาเนื้องอกส่วนที่เหลืออยู่ออกได้ จากการศึกษานี้แสดงให้เห็นว่า การรักษาผู้ป่วยมะเร็งเต้านมระยะลุกลามที่ไม่สามารถผ่าตัดเอาก้อนเนื้องอกออกได้และยังไม่มีการแพร่กระจายของโรคไปยังอวัยวะอื่นด้วยการฉายรังสีร่วมกับการอบความร้อน และอาจร่วมกับยาเคมีบำบัดด้วยนั้น เป็นการรักษาที่สามารถลดอาการเจ็บปวด หยุดเลือดออก และลดแผลอักเสบจากเนื้อตายได้อย่างมีประสิทธิภาพและปลอดภัย นอกจากนี้ยังมีโอกาสควบคุมโรคได้โดยเฉพาะเมื่อใช้ร่วมกับการผ่าตัด

คำสำคัญ : มะเร็งเต้านม, การรักษาด้วยความร้อน, การฉายรังสี

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