

# Re-Differentiation Inducing Treatment for Cancer

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## Abstract

**Background:** For a long time, oncologists have believed that the main factors causing carcinogenesis are genetic abnormalities or protracted mitochondrial respiratory degeneration. However, in my previous study, I have confirmed that mitochondrial respiratory degeneration is the true causal factor of carcinogenesis. In this study, I will show that defective mitochondria can be treated using re-differentiation inducing treatment that can restore damaged mitochondria to normal mitochondria.

**Methods:** I have summarized the medicines and methods that are effective for restoring mitochondrial function and mitochondrial replication. There-differentiation-inducing treatment is the combination of vitamin A, high dose vitamin C, solcoseryl, cyclic AMP and specific herbal medicine (SA) and hyperthermia. This treatment was applied to those patients who were difficult to treat by authorized treatment.

**Results:** Patients with advanced cancer who were treated with the re-differentiation-inducing treatment showed remarkable improvements, and there were no recurrence of cancer for many years. Furthermore, patients received hyperthermia when the former treatment was not effective.

**Conclusion:** Carcinogenesis is caused by the dysfunction of damaged mitochondria. Therefore, the re-differentiation-inducing treatment by the combination with vitamin A prescription, high dose vitamin C, Solcoseryl, cyclic AMP, herbal medicine (SA) and hyperthermia were thought to restore the functioning of the defective mitochondria to that of normal mitochondria.

**Keywords:** Carcinogenesis; Mitochondrial degeneration; Herbal medicine specifically to inhibit cancer cell respiration; Defective immune-surveillance; Re-differentiation-inducing treatment.

## Introduction

Sixty years ago, Otto Warburg initially proposed that aerobic glucose fermentation was an epiphenomenon representing one of the most fundamental problems in cancer biochemistry. That is damaged mitochondrial respiratory dysfunction. However, I have confirmed that core carcinogenesis is definitely caused mitochondrial respiratory degeneration by using specific herbal medicine (Sun Advance).

Koura H. et al. experimented with the hybridization of enucleated normal cells with cancer cells and they showed that the hybridized cell (cybrids) reverted to normal cells because cytosolic mitochondrial factors played the most important role in cell hybridization. Researchers who insist that carcinogenesis is induced by the accumulation of genetic abnormalities have neglected the results of these hybrid's (cybrids) experiment as described below<sup>[1-3]</sup>(Fig 1).

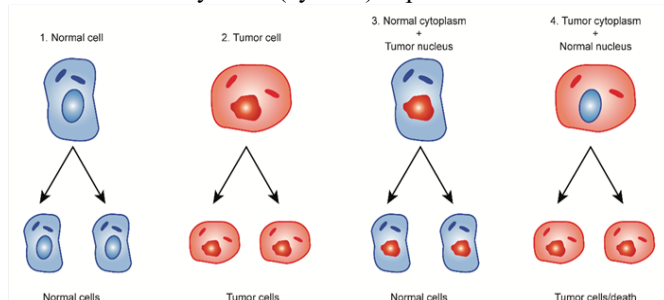


Figure 1: Cybrids experiment cited from Koura et al.

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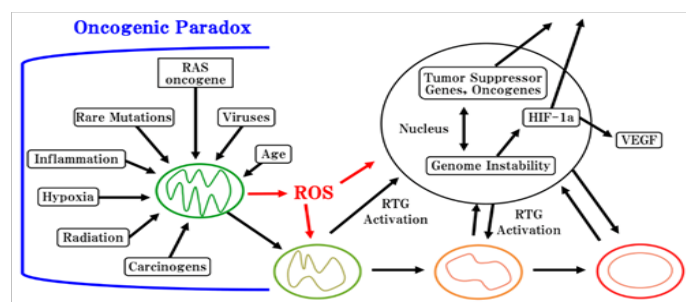
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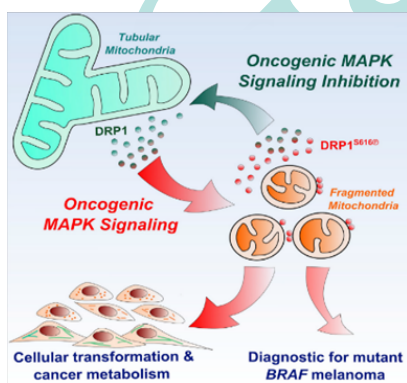
Seyfried reported that normal mitochondria maintain a differentiated state, thereby suppressing carcinogenesis, whereas dysfunctional mitochondria can enhance dedifferentiation, thereby facilitating carcinogenesis<sup>[4-8]</sup>.



**Figure 2:** Oncogenic paradox, mitochondrial degeneration processing and downstream of genetic change cited from Thomas Seyfried

He reported that carcinogenesis is a protracted form of mitochondrial dysfunction and indicated that genome abnormality occurs as a down-stream of mitochondrial dysfunction (Figure 2).

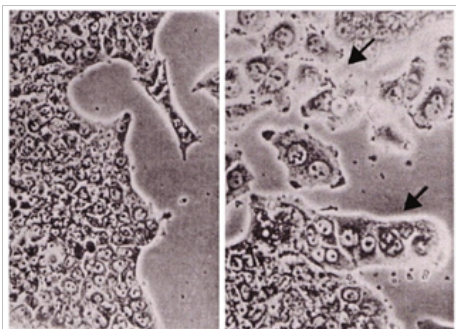
Serasinghe et al. reported that mature mitochondria are changed to degraded or fragmented mitochondria by oncogenic MAPK signaling, and from fragmented mitochondria are changed to mature mitochondria by oncogenic MAPK signaling inhibition<sup>[9]</sup>.



**Figure 3:** From mitochondrial maturation to mitochondrial fragmentation vice versa are reversible cited from M.N. Serasinghe

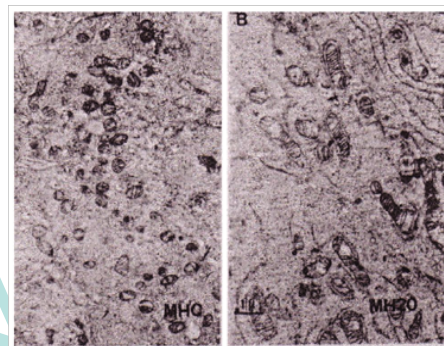
This mitochondrial reversible change may be correlated with the mitochondrial change above mentioned.

Arichi reported that the addition of Panax Ginseng saponins (20µg) induces re-differentiation of Morris hepatoma cells into normal liver cells after 2 months<sup>[10]</sup>. (Figure 4)



**Figure 4:** Morris hepatoma cells re-differentiated into normal liver cells with the addition of Panax Ginseng cited from Arichi et al.

In this experiment, electron microscopic photographs clearly showed that the shrunken mitochondria were re-differentiated into normal mature mitochondria. The segregated smaller mitochondria reverted to normal mature large mitochondria after the addition of Panax ginseng saponins (20µg) in the next Figure 5.



**Figure 5:** According to the re-differentiation of hepatoma, the fragmented mitochondria changed to mature mitochondria cited from Arichi et al.

The Panax ginseng experiment also suggested that there was no correlation between the re-differentiation of Morris hepatoma cells and gene abnormality in cancer cells. Cancer cells can be induced to undergo re-differentiation. In this study, re-differentiation inducing treatment was prepared using vitamin A, high dose vitamin C, solcoseryl, cyclic AMP, a herbal medicine (SA) and heat shock protein (HSP). The combination was used for this treatment for the following reasons.

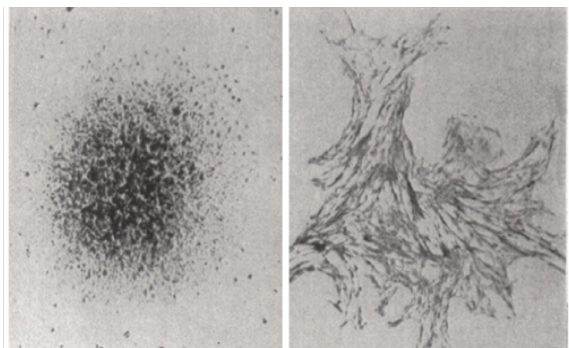
- Vitamin A ( $5 \times 10^4$  units) injection(ic) was administered because the serum of cancer patients generally display low concentrations of vitamin A and a shortage of vitamin A- binding protein in those serum<sup>[11-13]</sup>. Furthermore, vitamin A has the ability to differentiate juvenile cells to differentiated cell.
- High dose of vitamin C (30-70 g) were administered to increase the hydrogen peroxide concentration in cancer cells<sup>[14,15]</sup> and to suppress their growth.
- Solcoseryl (2ml/1A) extracted from the hemolyzed blood (SS-094) of young cattle<sup>[16]</sup> was administered because it promotes mitochondrial function and wound healing and corrects the glycolytic cycle in hypoxic microenvironments.



**Figure 6**

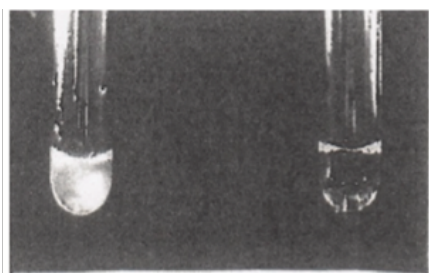
- A combination of an intravenous dripping infusion of cyclic AMP( bucladesine sodium 300mg/1A) was used to correct the defective immune-surveillance of cancer patients' sera<sup>[17]</sup> by maintaining appropriate concentrations of cyclic AMP. Cyclic AMP needs calcium as a second hormonal messenger and a medium with a low calcium concentration is conducive in carcinogenesis.

Hsie demonstrated that the addition of 1mM of cyclic AMP led to the re-differentiation of ovarian cancer cells into normal fibroblasts within 5 hours<sup>[18]</sup>. This cellular morphological change was directly induced by cyclic AMP in damaged mitochondria or microtubules.



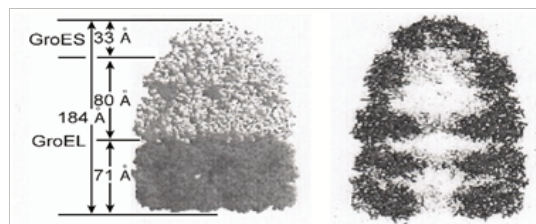
**Figure 7:** Ovarian cancer cells re-differentiate into normal fibroblasts in the presence of cyclic AMP cited from A.W. Hsie.

- e) A herbal medicine (SA)<sup>[19,20]</sup> was used for preventing carcinogenesis and preventing onco-virus transformation and excluding immunosuppressive substances from the body because of inhibiting effect on the oxidative respiration of cancer cells (1.5g/day).
- f) When these treatments were not sufficient, hyperthermia treatment was administered to produce ample HSP molecules in the lymphocytes and cancer cells. Hyperthermia treatment is effective for treating cancer neoplasms because of the structure of cancer blood vessels<sup>[21-24]</sup>. We must importantly remind that natural spontaneous regression of cancer has been observed after long-lasting episodes of unknown fever in most prevalent cases. As shown in below, boiled chicken egg protein becomes aggregated and turns white after treatment at 70° for 10 min (left tube).



**Figure 8:** Function of HSP: Left tube without HSP, right tube with bacterial HSP

However, when bacterial HSP was added to the chicken egg protein before treatment at 70°C for 10 min (left tube), and no aggregation was observed (right tube). This experiment confirms that the chicken egg protein aggregation was protected by the addition of bacterial HSP. Nevertheless, the HSP is just a protein cradle because its functions are related to the management, degradation, maintenance and reproduction of damaged proteins. Electron microscopic image of HSP is shown in below Figure 9<sup>[25]</sup>. Mitochondrial HSP functions as a shaperone and mediates essential functions for mitochondrial biogenesis such as the import and folding of proteins.



**Figure 9:** HSP molecule has cradle shape cited from Siglaer P.B. et al.

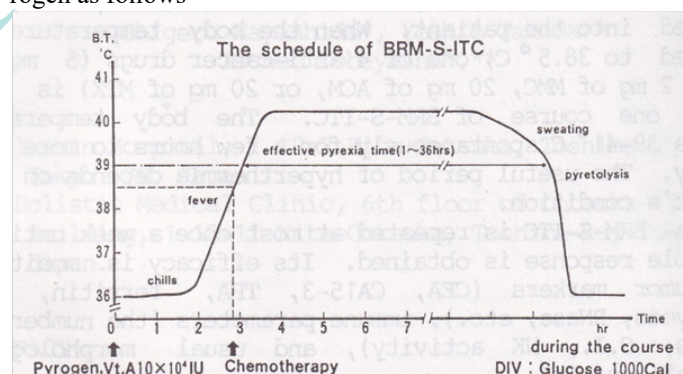
Heat treatment induces an increase in intracellular cyclic AMP concentrations in cancer cells<sup>[26,27]</sup> and this HSP has also been reported to function in the differentiation and evolution of cells<sup>[28]</sup>.

For systemic hyperthermia, the following menu (A) and style (B) were used.

(A) Short time whole body hyperthermia (WBH) utilizing far-ultra red rays

- 1) Injection of vitamin A (5~10x10<sup>4</sup> units) intra-muscularly.
- 2) Glyceol infusion when metastasis of brain is existing
- 3) 100 ml of physiological sodium saline contained 5~10 mg of CDDP
- 4) Soldem AG (Terumo) 500 ml + Actosin (bucladesine sodium 300mg/1A) 1A + Solcosery l(SS-094)(2ml/A) 2A
- 5) Fructlact 500 ml +VC 20mg +Neophagen 1A+Pantosin 1A+ 10NaCl + Sodium bicarbonate 1A
- 6) 100ml of physiological sodium saline + digoxin 1/2 A
- 7) 100 ml of physiological saline + Serenace (haloperidol)
- 8) (100 ml of physiological saline + Contomin (chlorpromazine)1A x (n)
- 9) Fructlact 500 ml + VC 30 g + 10% NaCl(1A) + Sodium bicarbonate 4A
- 10) Fructlact 500 ml + VC 20 g + 10% NaCl (1A) + Sodium bicarbonate; 3A
- 11) 100 ml of physiological saline + Laennec (human placental extract) (3~5A)

(B) BRM-systemic immune-thermo-chemotherapy utilizing pyrogen as follows



In this study, I have showed that dysfunctional mitochondria can be treated using re-differentiation-inducing treatment, which restores the damaged mitochondria.

### First case report

The first case is that of a 48-year-old man who was diagnosed

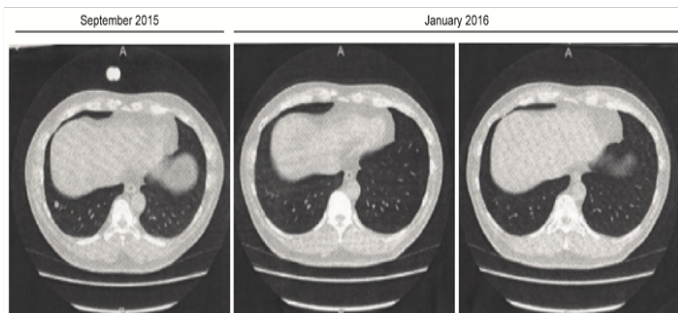
with recurrent leiomyo sarcoma as pathological diagnosis on the upper right hand. After surgical resection (27, May, 2015), the sarcoma metastasized to the lung in September, 2015. Chemotherapy was performed with doxorubisin (126 mg), but it did not disappear even December, 2015. Thereafter, the patient visited my hospital, and he subsequently received the re-differentiation-inducing treatment once a week. (Figure 10)

### Second Case Report

The second case is that of a 30-year-old woman who had undifferentiated ovarian cancer and her pathological diagnosis was undifferentiated germinoma. She underwent ovarian resection twice. After resection, she underwent chemotherapy four times. Thereafter, she visited my hospital and underwent tumor marker-inducing examination utilizing a combination of vitamin A and hyperthermia<sup>[29-31]</sup>. The following data were recorded: CEA: 2.2 ng, ΔCEA which means the width of changing data during 48 hours; 1.0 μg Ferritin (FT); 160 μg (ΔFT: 40 μg) , FT/ Fe = 2.2, ΔFT/Fe = 0.6, LDH: 294(ΔLDH =41U), Ribonuclease (202 U), α1-golbulin: 3.5%, Albumin (64%) T cell number (1468), stimulation index (173), and NK cell activity (17.8%)

She was diagnosed with TS (V): gram level cancer: G2 (clinical level): cancer stage II according to cancer risk assessment method by TMCA which was reported in cancer (1994)<sup>[32]</sup>. Then, she underwent a PET examination, which revealed Virchow lymph-node metastasis in the right side. The patient subsequently received herbal medicine (SA; 1.5g/day) by oral intake and detoxifying refreshment treatment<sup>[33]</sup> one time a week and dietary energy restriction of glucose and glutamine for 6 months and the clinical findings indicated that she had improved into normal range showed below Table 2. The patient was followed for 19 years and her cancer had never recurred. The patient's TMCA data are currently as follows: Thymidine kinase: 7.7, α1-globulin fraction (2.6%), albumin( 61.1%), LDH(238)

In addition, her present risk assessment was classified into TS (III).



**Figure 10:** The left photograph shows a CT scan taken in September, 2015, center and right photograph show the CT scans taken in January and March, 2016. As shown in CT image, metastasis has clearly disappeared after January 2016.

The patient's initial risk assessment according to the TMCA was classified as tumor stage V (= G2), whereas, in July 2017, all the data ferritin, FT/Fe, thymidine kinase, α1-globulin fraction were restored to normal range after processing of the treatment. TMCA risk assessment was classified as TS(III) on June,2016, above shown. There has been no recurrence of cancer for the past 3 years after he received the re-differentiation inducing treatment.

**Table 1**

| Time course         | 28/Dec/2015, | 14/Jan, | 18/Feb, | 17/March, | 19/April, | 13-Jun  |
|---------------------|--------------|---------|---------|-----------|-----------|---------|
| Ferritin (FT)       | 489          | 337     | 186     | 225       | 195       | 208     |
| Serum iron (Fe)     | 75           | 67      | 46      | 78        | 71        | 85      |
| FT/Fe               | 6.5          | 5       | 4       | 2.8       | 2.7       | 2.4     |
| Thymidine kinase    | 59.1         | 4.9     | 2.1     | 3.6       | 3.1       | 4.5     |
| α1globulin fraction | 3            | 2.6     | 2.6     | 2.4       | 2.4       | 2.40%   |
| Albumin             | 60.7         | 60.4    | 62.3    | 60.7      | 60.2      | 61.10%  |
| Risk assessment:    | TS(V:G2)     | TS(IV)  | TS(IV)  | TS(III)   | TS(III)   | TS(III) |
| CT finding:         | +            | ---     |         |           |           |         |

**Table 2**

|                   | Oct(1999)               | July(2000)             | Jan(2001) | Feb(2002) | Jan(2005) | July(2015) |
|-------------------|-------------------------|------------------------|-----------|-----------|-----------|------------|
| RNase:            | 202 U                   | 147                    | 111       | 99        | 99        |            |
| Thymidine Kinase: |                         |                        |           |           |           | 7.7        |
| Albumin:          | 64%                     | 67.4                   | 65.1      | 65.2      | 62.9      | 61.1       |
| α1-globulin:      | 3.50%                   | 2.9                    | 3         | 2.9       | 2.9       | 2.6        |
| NK activity:      | 17.80%                  | 24                     |           | 66        |           |            |
| Risk assess:      | TS (V)(G <sup>2</sup> ) | TS(V)(G <sup>1</sup> ) | TS(IV)    | TS(IV)    | TS(IV)    | TS(III)    |

### Third Case Report

The third case is a 32-year-old male with stage-four, adenomatous lung cancer. We carried out re-differentiation inducing treatment once a week for 3 months because his NK activity was high (80.7%). Further, the patient received detoxification therapy 10 times and fasting therapy with vegetable juice and daily 10 km walks for 3 months. Pleural metastasis was observed in this patient before treatment, but the lung metastasis disappeared at 3 months after the application of the re-differentiation inducing treatment and herbal medicine(SA), retinoic acid (50000 units) and fasting therapy with vegetable juice.

The following data show the biochemical examination in this patient over 2 years (Table 3).

The CT photograph on the left side shows the condition before treatment, and CT image on the right side shows the condition after 3 months of treatment. The pleural metastases have disappeared completely(Fig 11).

Table 3

|                   | 2017     |        | 2018    |
|-------------------|----------|--------|---------|
|                   | Sept, 12 | Oct, 2 | Jan, 18 |
| CA19-9:           | 595      | 229    | 22.1    |
| CEA:              | 113      | 200    | 6.2     |
| NCCST439:         | 31.3     | 19     | 4.3     |
| SLX:              | 74       | 50.8   | 34.2    |
| Thymidine Kinase: | 11.6     |        | 5.2     |
| Albumin:          | 58.4     | 67.1   | 67.4    |
| $\alpha$ 1-g1:    | 3.2      | 2.4    | 2.1     |
| $\gamma$ -gl:     | 16.4     | 14.9   | 14.2    |
| LDH:              | 187      | 190    |         |
| VitaminA:         | 509      | 722    |         |
| T cell number:    | 802      |        |         |
| SI:               | 41       |        |         |
| NK cell:          | 80.70%   |        |         |

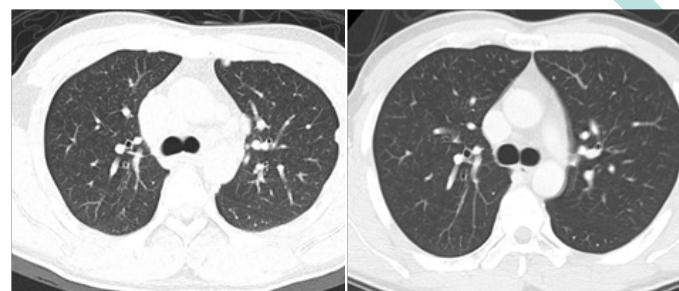


Figure 11: This male of CT image, left before treatment, right after treatment (3 months)

Table 4

| Date (TM)                    | 1991 | 1991 | 1992 | 1993 | 1994 | 1995 | 1999  |
|------------------------------|------|------|------|------|------|------|-------|
| BCA225:                      |      | 207  | 212  | 336  | 179  | 227  | 221   |
| CA15-3:                      |      |      |      | 33   | 16   | 21   | 19    |
| $\alpha$ —1globulin /Albumin |      | 3.5  | 3.4  | 2.6  | 3    | 2.5  | 2.50% |
| $\alpha$ ~1/Albumin          |      | 61   | 59.8 | 59.5 | 61.8 | 60.2 | 64.8  |
|                              |      | 5.7  | 5.6  | 4.3  | 4.8  | 4.1  | 3.8   |

### Fourth Case Report

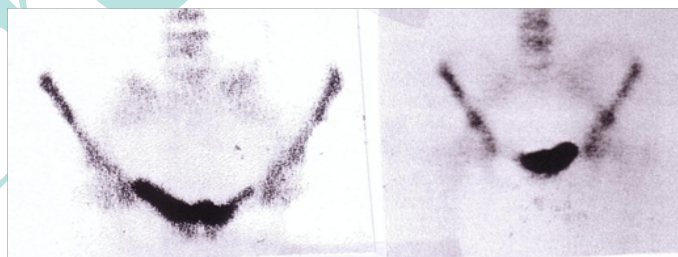
This is the case of a 42 year-old woman who developed mammary cancer in December, 1990 and received surgical operation immediately. The cancer recurred and metastasized to bone metastasized and skin invasion after mammectomy. Regional recurrence and pubic bone metastasis were observed on October 2, 1992. This patient received differentiation-inducing treatment and hyperthermia 46 times.

Tumor maker BCA225 increased from 324 to 420 and  $\alpha$ 1-globulin fraction was elevated to 3.5%.

Not only tumor markers, but also the ratio of  $\alpha$ —1globulin fraction/ Albumin were improved.



The left picture shows the local recurrence on 24 September,1991. The right picture shows the skin of the same part 9 years later after treatment of 46 times of systemic hyperthermia. Biochemical data showed that BCA225 became to 221 and  $\alpha$ —1globulin fraction became within normal range (2.5%) on 25 February, 1999. There has been no recurrence 20 years later.



The left image shows the bone scintiphotograph taken on 21 January, 1992. There was a hot spot in the pubic bone. The right image shows the bone scintiphotograph taken on 9 April, 1999. The pubic bone metastasis disappeared. There is no recurrence after 20 years later.

## Fifth Case Report

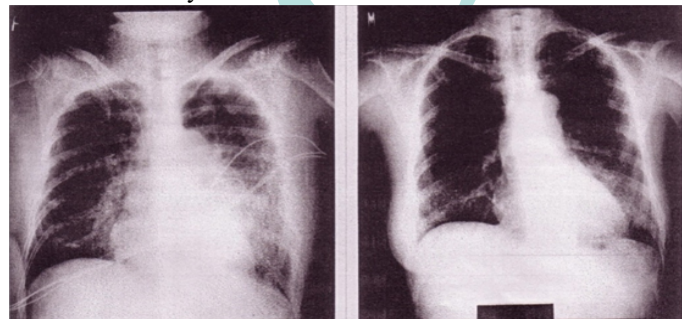
The fifth case is that of 48-years -old woman with bone metastasis for grave stadium of advanced cancer after surgical extirpation of breast tumor. She was diagnosed with mammary cancer in April, 1995. She developed difficult in walking because of hypercalcemia (calcium concentration:16 mg/dL) and metastasis. Bone metastasis was observed in all the bones of the body. Pathological bone fracture occurred in 7 ribs. Respiration also became difficult. Osteoclastic changes occurred on vertebrae Th12 because of bone metastasis. Therefore, it was difficult for her to walk and her family brought her with wheelchair. Although her condition was serious, she asked me for her forcibly to treat with 24 times of systemic hyperthermia.

With a result that her condition was much improved so that she was able to walk by November, 1995. The left chest radiograph shows the chest condition at the time when she came to my hospital for the first time. The right chest radiograph shows improvement in cardiac insufficiency.

Table 5

| Date    | 1995    |         |         |        |
|---------|---------|---------|---------|--------|
| TM      | 7, June | 14, Aug | 4, Sept | 6, Nov |
| CA12-5: | 77      | 80      | 62      | 23     |
| TPA:    | 394     | 316     | 301     | 76     |

All the tumor markers showed improved results. After 6 months, she could walk by herself.



Before treatment, 6 months after treatment

## Results

This study showed that the re-differentiation inducing treatment with the combination with vitamin A, high dose vitamin C, solcoseryl, cyclic AMP, specific herbal medicine (SA), and hyperthermia reduced the recurrence rate of cancer and the overall physiological condition of the patients with cancers. Moreover, this study shows that carcinogenesis occurs due to mitochondrial respiratory degeneration and that carcinogenesis is reversible. Since, carcinogenesis is caused by mitochondrial respiratory dysfunction, patients with cancer should be treated using a re-differentiation inducing treatment methods.

## Discussion

We could carry out non-invasive treatment for advanced cancer. During the hyperthermia, we have utilized a small amount of

chemotherapy, e.g. CDDP, 5~10mg, not for the aim of chemotherapy, but as the thermosensitive agents. These small amounts of chemotherapy have no side effects, but hair will grow up for those patients who have fallen out their hair after chemotherapy.

## Conclusion

As carcinogenesis is mitochondrial respiratory degeneration. So, we can treat cancer patients by re-differentiation inducing methods.

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