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Conference Paper

Cases That Respond to Oncothermia Monotherapy

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This Conference Paper is based on a presentation given by Tae Sig Jeung at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

There is a long history of hyperthermia in oncology, but its wide range acceptance and application are missing even today. A new approach of oncological hyperthermia, oncothermia, looks promising modality of the complementary treatment of advanced malignant cases. Our present paper is targeting this method, trying to answer the question of its feasibility to treat various advanced cases in monotherapy process, as well as its applicability for a long, large number of treatment sessions protocols.

1. Background

Although the hyperthermia was among the very first medical treatments in human medicine, this approach has ambivalent evaluation as a therapy. Hyperthermia is one of the most common therapies in "house" applications, a part of the "popular wisdom" of the traditional medicine. Heat is applied according to unwritten traditions in every culture. Heat treatment has high popularity in Korea for various preventive or curative intentions. It is applied for simple prevention or "cure" of common cold, applied to still various pains (joints, muscle spasms, various orthopedic problems, etc.). Heat is applied for better overall conditions and for simple relaxing or sometimes for spiritual reasons. The various heat therapies are commonly used complementarily with natural drugs (tees, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural, and social events (ritual hot bath cultures) or to long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

These popular treatment applications of heating are types of "kitchen medicine": the old recipes are "sure," the patient takes it, and cured when it is done according to the auricular traditional regulations. This "for sure" is the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, "do it, get it." However, the hyperthermia is not as simple as the traditions interpret it.

Internal source of heat is the fever as a reaction to infections [1] or pyrogens [2] or malignant hyperthermia [3] as well. The natural fever is induced by the living system [4]. The situation is quite different, when the heating is forced from outside of the body, and it is intended to be applied as therapy. The forced heating works against the homeostasis, and the body tries to keep the temperature normal, irrespective that the heating is local, regional, or systemic. The interpretation of hyperthermia as therapy has various stumbling blocks, because the effect caused by the absorbed heat is too complex: the applied, absorbed energy is usually depleted nonhomogeneously, and the intricacy of the living processes modifies the intended motive of application. Further complication is in the heating process itself: the efficacy certainly differs by heat sources and by the properties of the target volume and its physiological effects as well.

A frustration in understanding of the differences between the natural and constrained heat therapies and their consequent reactions characterizes the complete history of hyperthermia in medicine and explains in majority why hyperthermia has no well-deserved place in the professional medical armory to treat various diseases.

Hyperthermia as a treatment modality is battling for the step from the biomedical experiment status to a clinically proven one [5, 6].

The central problem of the forced heating in a local/regional volume is the physiological feedback reaction acting to compensate the compulsory temperature elevation. The main physiological feedback mechanism is the active blood flow in the heat-targeted volume [7–9]. The intensified blood flow is excellent heat exchanger, cooling down the heated volume and effectively increasing the temperature in the surroundings of the target. The high blood flow delivers extra nutrients (mainly glucose) supplying the tumor as well as increases the risk of dissemination of malignant cells by the blood stream. Both effects are contrary to our direct aim to destroy the cancer. The situation is a competition now between the cellular distortion by direct heat and the supply of the growth of the tumor together with its increasing dissemination ability. This is the origine of the contradictiog results and the missing satisfactory control on the oncological heat treatments.

Technically, a huge variety of heating could be applied by heat therapies [10]. Its energy production, its selectivity, locality, kind of energy delivery, locality invasivity control, and applied frequency of the electromagnetic waves, as well as their medical applications and combination with other methods make the heat therapies different.

Oncothermia is a special heating, targeting the membrane of the malignant cells [11]. This nanorange heating makes it possible to destroy the malignant cells by extreme temperature gradient on their membranes individually [12], without exciting of the physiological feedback mechanisms, without considerable blood flow increase.

Our objective in this paper is to show actual cases of how oncothermia works. The main addressed questions are as follows.

(1) Which adverse effects does oncothermia have by dose escalation (extended treatment duration)?

(2) How is the long treatment effective in various cases of the disease?

(3) Can we apply oncothermia as monotherapy for a long time?

(4) Are we able to handle the fatal cancer cases as chronic disease in the style of dialysis?

2. Method

There were chosen numerous cases, having complications with the gold-standard therapies, in high-line treatments. Oncothermia was applied or complementary to chemo- and/or radiotherapy or it was applied as monotherapy in the cases when the combination was not feasible. The study started in December 2011 and summarized the results until September 2012.

Patients were the intention-to-treat (ITT) population; no cohort was formed, a retrospective data-collection is the basis of the evaluation. The study was performed in single-institute basis, and the patients were rigorously diagnosed, checked, and followed up during the trial. All together 216 patients were treated in this time with 4263 sessions cumulatively. From this, we had chosen 16 cases characteristically showing the results.

We used the EHY2000+ device (Oncotherm GmbH, Germany), applying the 20 and 30 cm diameter electrodes in step-up heating protocol. The maximal energy was 150 W; duration of a session was 60 min each, 2~3 times/week, and 12 times in one cycle. The average number of the treatments was 33 sessions or 4 cycles; the duration of the time of the full cycles was over 6 months.

3. Case Reports

3.1. Rectosigmoid Cancer with Liver Metastasis. A 43-year-old Asian man was diagnosed with Rectosigmoid cancer with metastasis of liver in March 10, 2012. And T-loop End Colostomy was performed on May 7, 2012. Avastin-FOLFOX chemotherapy was given 3 times after operation and the second-line FOLFIRI chemotherapy was given 3 times. He received radiotherapy to liver delivering 18 Gy in 10 fractions for 2 weeks from August 13, 2012 to August 27, 2012 and concurrent 37 times oncothermia from July 20, 2012 to November 21, 2012 (see Figure 1).

Tumor mass in liver regressed, and liver parenchyma increased gradually with concurrent small dose of radiation and oncothermia. No adverse effect that originated from oncothermia was observed. This result gives the large possibilities of combined treatment of oncothermia with low dose of radiation for far advanced cancer for palliative treatment.

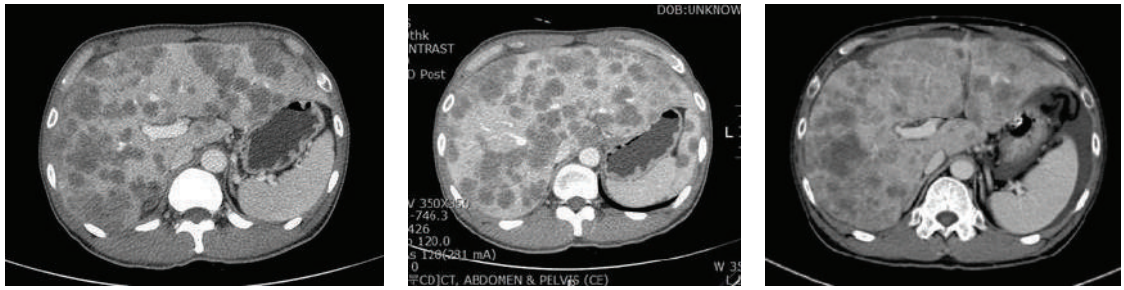
3.2. Hepatocellular Carcinoma. A 61-year-old Asian man was diagnosed with hepatocellular carcinoma. TACE was given on February 17, 2011. He suffered from type B virus hepatitis from 1992 and liver cirrhosis from 2001. TACE could not be given anymore after one time even though HCC was aggravated with elevation of alpha-fetoprotein level in serum. Regrowing cancer and rapid rising of alphafetoprotein (20.48 to 448.90) appeared in November 2011.

Twenty four times of oncothermia were given from November 21, 2011 to February 27, 2012 (see Figure 2).

Alpha-fetoprotein level was lowered and kept stable at 24.39 after oncothermia to July 2012. Tumor mass was stable until new lesion in liver found in September 2012 with the high elevation of alpha-fetoprotein to 697.40 after 7 months from oncothermia.

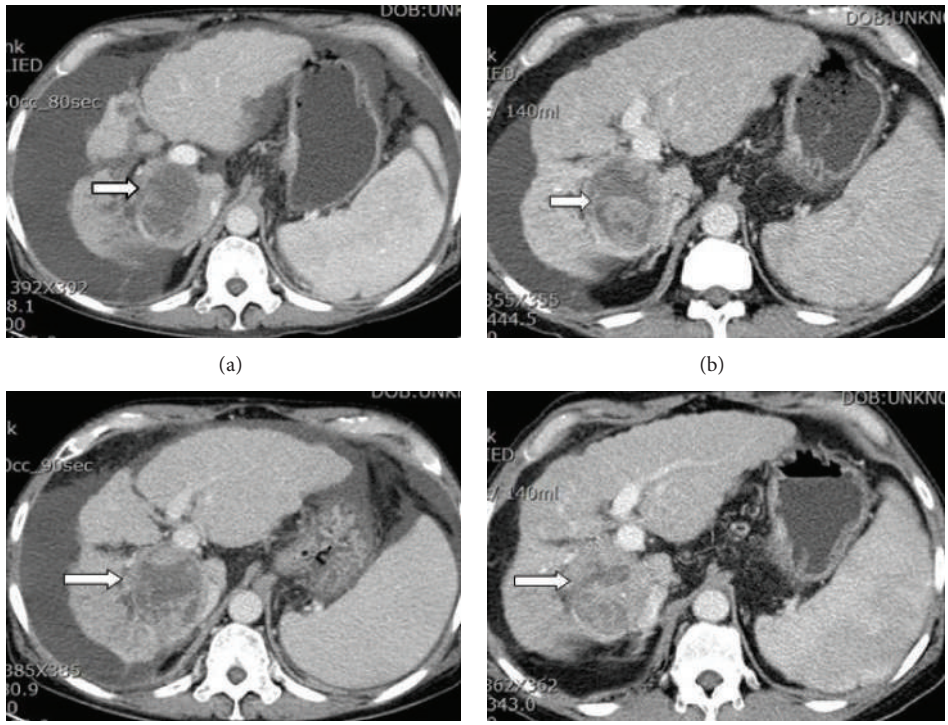
3.3. Pancreatic Cancer. A 59-year-old Asian woman had been diagnosed with Pancreatic cancer in August 2010. Chemotherapy was given many times as much as possible at other hospitals.

She visited Kosin University first in August 2011 just only to relieve massive pain for serious carcinoma peritonei with conglomerated mass attached at anterior abdominal wall. Radiation therapy was given 30 Gy in 10 fractions (once/day, for 2 weeks) with IGRT technique to anterior abdominal wall mass in August 2011. Ascites was not at that time.



(a) (b) (c)

Figure 1: (a) Before oncothermia. (b) After 12 times of oncothermia. (c) After 31 times of OncoTx.



(a) (b)

(c) (d)

Figure 2: (a) Two months before oncothermia. (b) Just before oncothermia. (c) After 24 sessions of oncothermia. (d) Seven months after oncothermia.

Abdominal pain was relieved much just after palliative radiation therapy but progressed gradually from October 2011.

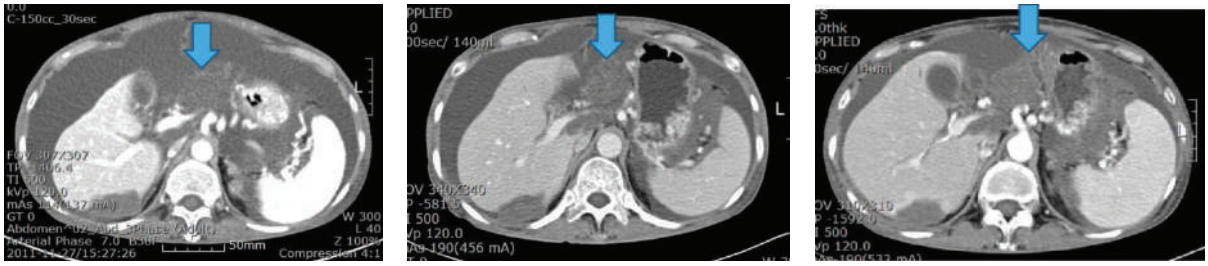
Ascites and intestinal obstruction were developed. Intestinal bypass surgery was recommended by surgeon but was not performed. It was difficult to recover from the high risk of the operation since the patient had far advanced cancer and poor general condition.

Oncothermia was started firstly in our hospital as soon as it was installed in November 2011. She could eat some food, and ascites was controlled by medicine since 5 times of oncothermia were given. Cancer mass regressed a little bit. Amount of analgesics intake was reduced.

She maintained well with oncothermia to later June 2012. But her cancer became worse gradually. Eventually, cancer metastasis to both pleural cavities was developed with both pleural effusions. Patient's general condition became worse gradually for pleural metastasis that was drained often to reduce dyspnea. It was difficult to keep hyperthermia for 1 hour due to the poor general condition, and inevitably carcinoma peritonei became worse from August 2012.

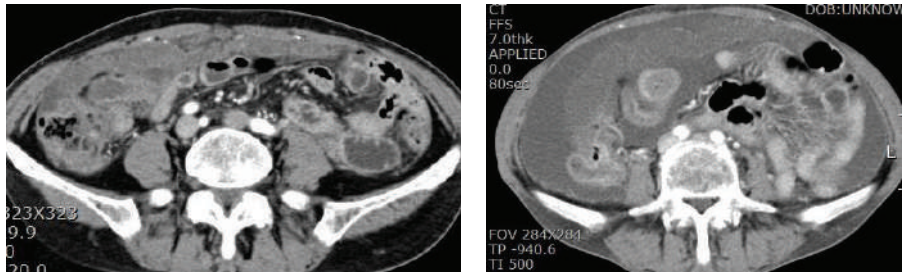
She died due to pneumonitis with massive pleural effusion on the early September 2012 (see Figures 3, 4, and 5).

Although she had a massive abdominal pain because of far advanced carcinoma peritonei, she lived for 10 months by controlling the massive abdominal pain with oncothermia.



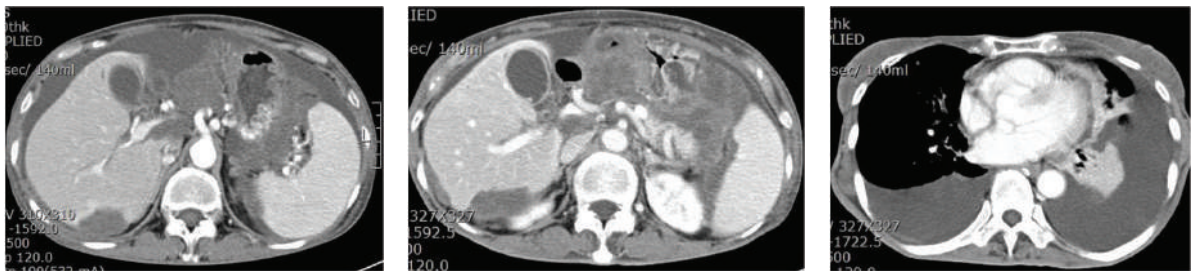
(a) (b) (c)

Figure 3: (a) Before oncothermia. (b) After oncothermia (30 sessions). (c) After oncothermia (60 sessions).



(a) (b)

Figure 4: (a) July 7, 2011. (b) October 16, 2011.



(a) (b) (c)

Figure 5: (a) May 15, 2012. (b) July 17, 2012. (c) July 17, 2012 (2).

She was the first patient to be applied oncothermia. From her case, there are many possible cases applied to other patients of advanced cancer with oncothermia without any negative side effects.

A total of 82 times of oncothermia were given to her by 2~3 times/week for 10 months. It can be possible to apply many times of oncothermia for advanced cancer without any complications.

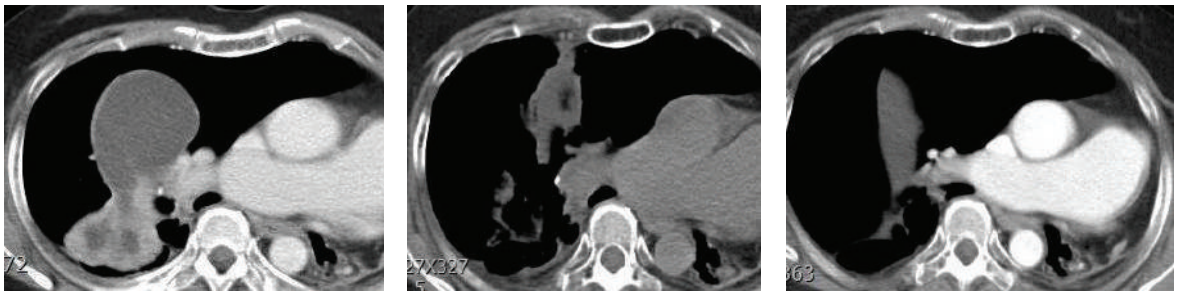
3.4. Synovial Sarcoma. A 48-year-old female was diagnosed with synovial sarcoma and received operation of the right thigh in 2004. She used to live well until the recurrent and metastatic cancer was discovered at the right lung in September 2011.

Radiation therapy 30 Gy in 10 fractions for 2 weeks to tumor mass at the right lung mass with IGRT technique was given carefully in April 2012. She lost the left lung by tuberculosis when she was young. Tumor mass regressed partially after radiation therapy but progressed in November 2011. She received 39 times of oncothermia from November 2011 to April 2012 (see Figure 6).

Metastatic sarcoma to lung markedly regressed with oncothermia. Sarcoma has been already known to be sensitive to hyperthermia. And also sarcoma is sensitive to oncothermia as well.

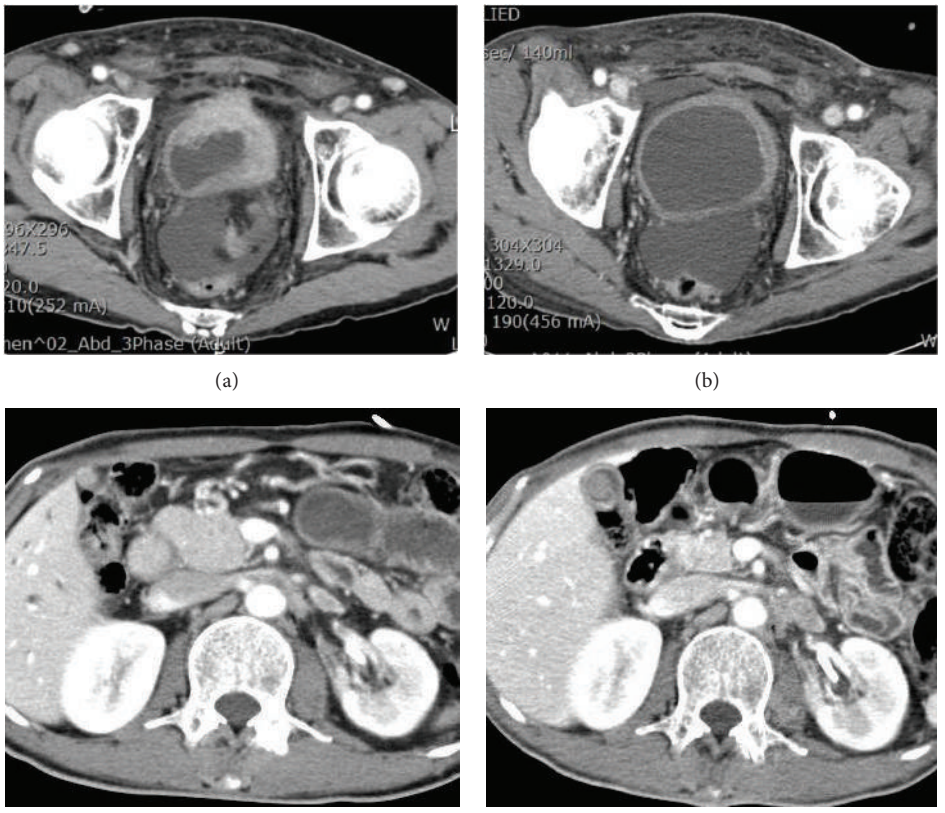
3.5. Pancreatic Cancer. A 49-year-old Asian man has been diagnosed with pancreatic cancer in November 2011. Chemotherapy was given in Mar 2012. Brain metastasis was developed, and 30 Gy radiation therapy in 10 fractions was given to the whole brain in March 2012. Urinary bladder metastasis was found in May 2012.

Twelve times Oncothermia (3 times/week) were given to pelvis for metastatic bladder cancer were given from May 14, 2012 to June 13, 2012. Twenty-six times were given



(a) (b) (c)

Figure 6: (a) Just before OncoTx. (b) Twelve times of OncoTs. (c) Thirty-six times of OncoTx.



(a) (b)

(c) (d)

Figure 7: (a) Before oncothermia. (b) After 12 times of oncothermia. (c) Before oncothermia. (d) After 12 times of oncothermia.

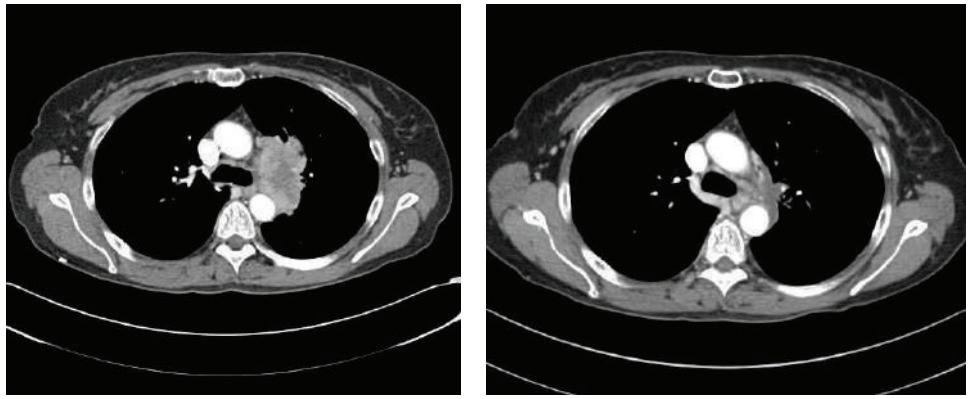
Oncothermia to pancreas from June 25, 2012 to August 30, 2012 (see Figure 7).

Metastatic bladder cancer regressed prominently after 12 times of oncothermia. Pancreatic tumor mass was also reduced in the size prominently after oncothermia. If the primary tumor was sensitive to oncothermia, metastatic cancer is also sensitive to the oncothermia. But she got sudden death on September 3, 2012 due to brain edema for aggravation of metastatic brain tumor.

3.6. Adenoid Cystic Carcinoma. A 56-year-old woman was diagnosed with adenoid cystic carcinoma of submandibular gland and received operation (mass resection and right marginal mandibulectomy and reconstruction with forearm free flap, Lt. and Lt. FTSG from Lt. forearm sural nerve graft) in June 1, 2009.

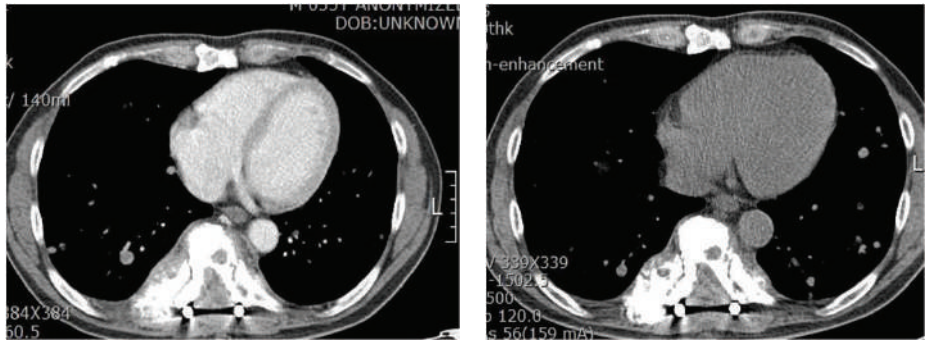
She used to live well up to finding recurrent cancer and metastasis to lung in May 2011. She refused any treatment like chemotherapy after she about the heard less effectiveness and great negative side effects of chemotherapeutic agent for adenoid cystic carcinoma. Dyspnea and blood-tinged sputum developed occasionally from May 2012.

She received radiotherapy delivering 30 Gy in 10 fractions (once/day) for 2 weeks in June 2012 and concurrent



(a) (b)

Figure 8: (a) May 31, 2012 (before OncoTx). (b) July 9, 2012 (after OncoTx & RTx).



(a) (b)

Figure 9: (a) Before HTx. (b) After 12 times of HTx.

48 times of oncothermia (2~3 times/week) from June 12, 2012 to October 2, 2012 (Figure 8).

Tumor mass at the left hilum was regressed markedly in chest CT scan after 24 times of oncothermia with 30 Gy of radiation therapy. Adenoid cystic carcinoma is generally resistant to radiation therapy. But concurrent radiotherapy and oncothermia made this metastatic lung cancer reduced in size.

3.7. Lung Cancer. A 55-year-old Asian man was diagnosed with lung cancer (adenocarcinoma) in March 2010 and received chemotherapy and target therapy.

He received radiotherapy at regrowing lesion with invasion to spine at the operated site and rib delivering 30 Gy in 10 fractions for 2 weeks in April 2011. Tumor mass regrew, and multiple metastatic lesions appeared in both lungs. Oncothermia was given 24 times (2~3 times/week) from April 10, 2012 to July 12, 2012 (see Figure 9).

Tumor mass was regressed at the right lung and spine. However, tumors progressed in the left lung because oncothermia was not given at the left lung.

Back pain to the right chest was subsided after oncothermia. Many cases showed the reduction of the metastatic bone pain with oncothermia.

It is possible to apply oncothermia to reduce metastatic bone pain with a variety of cancers.

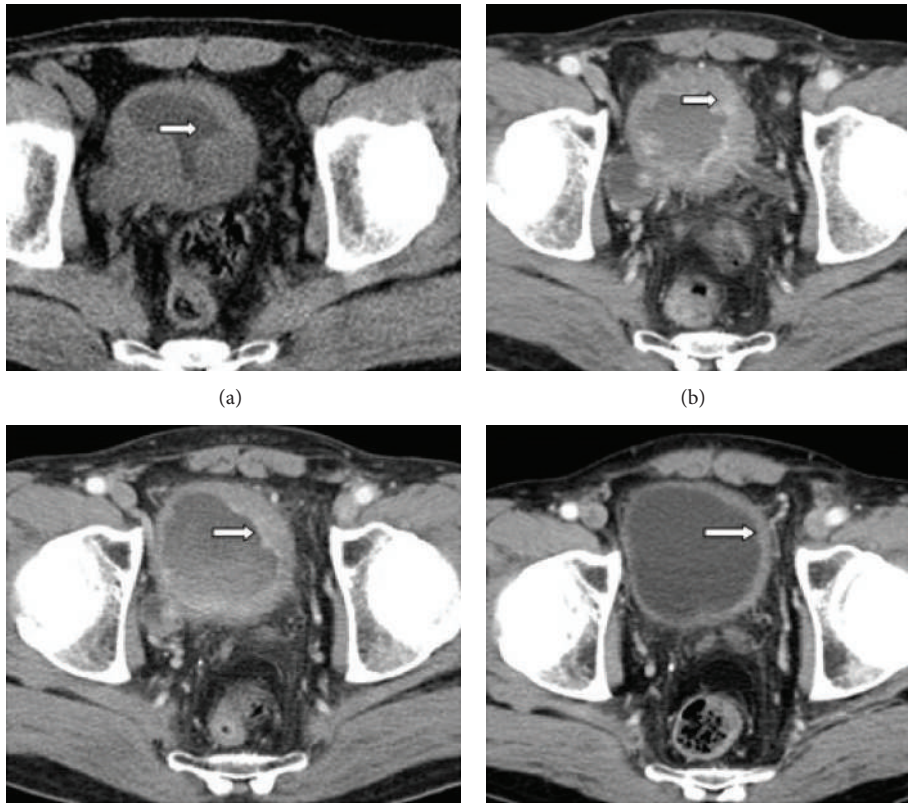
3.8. Bladder Cancer. A 67-year-old Asian man was diagnosed as bladder cancer (transitional cell carcinoma) in April 2008. Operation and 6 cycles of chemotherapy were performed in 2008.

Recurrent cancer in bladder was known in April 2011. Partial resection and chemotherapy were performed again after known recurrent cancer. But bladder cancer progressed in spite of chemotherapy in April 2012.

Twenty-four times of oncothermia were given from April 30, 2012 to July 31, 2012 (see Figure 10).

Tumor mass of bladder regressed after 24 times of oncothermia. As can be seen, the result of CT scan taken after 2 months stopped oncothermia; the further regression of the tumor mass was observed. That is, even though the oncothermia treatments were stopped, the effectiveness in the reduction of tumor mass was kept for 2 months.

3.9. Lung Cancer. A 47-year-old female was diagnosed as lung cancer (adenocarcinoma) in April 2010 Chemotherapy and target therapy were given up to October 2011. However,



(a) (b) (c) (d)

Figure 10: (a) Before oncothermia. (b) After 12 times of oncothermia. (c) After 24 times of oncothermia. (d) Two months after 24 times of oncothermia.

the patient was no longer affected by those treatments from the early December 2011.

Twelve times of oncothermia (2~3 times/week) were given from December 22, 2011 to February 2, 2012 (see Figure 11).

Tumor mass regressed markedly just after oncothermia. However, tumor mass progressed rapidly in 4 months of stopping oncothermia. Original tumor mass in the area of oncothermia was regressed. But new lesion at the outside of oncothermia region was progressed gradually.

She died in August 2012 due to liver, brain, multiple bone metastases, and massive aggravation of the lung cancer.

3.10. Pancreatic Cancer. A 68-year-old Asian man was one of the patients who received many times of oncothermia. Pancreatic cancer was diagnosed in August 2011. He refused chemotherapy from diagnosis. Operation was impossible to be performed at the time of the diagnosis. Oncothermia9@~3 Times/week) was given 65 times from February 16, 2012 to October 11, 2012 (see Figure 12).

He was treated with 65 times of oncothermia for pancreatic cancer without any negative side effects for 8 months.

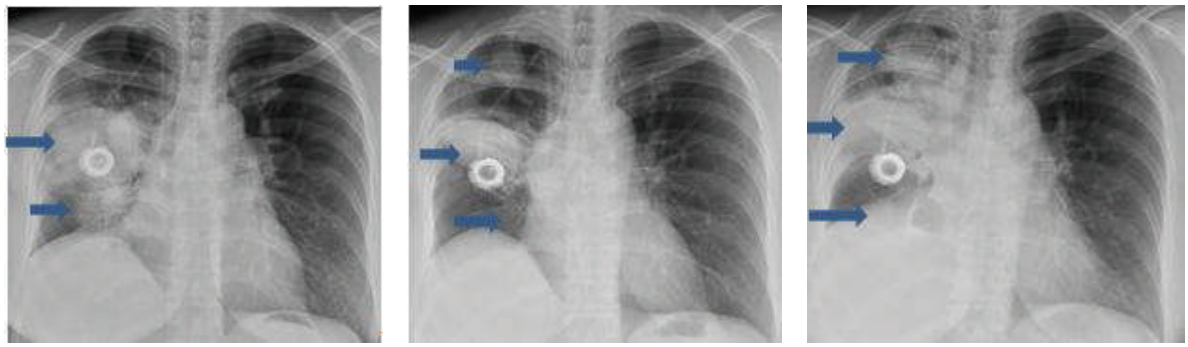
In the area of oncothermia treatment, the tumor mass was gradually reduced. However, tumor mass in the outside of oncothermia area was significantly increased. Therefore, oncothermia monotherapy is available to reduce pancreatic cancer.

3.11. Ovarian Cancer. A 70-year-old Asian woman was diagnosed with ovarian cancer, and RAH with both salphingo-oophorectomies was performed on October 6, 2011.

Cisplatin chemotherapy was given once just after operation. But she refused further treatment due to toxicity of chemotherapy. No special treatment was given from November 2011. Regrowing mass at the left ovarian site and carcinoma peritonei were known in January 2012. Oncothermia was given 12 times (3 times/week) from February 15, 2012 to March 19, 2012 (see Figure 13).

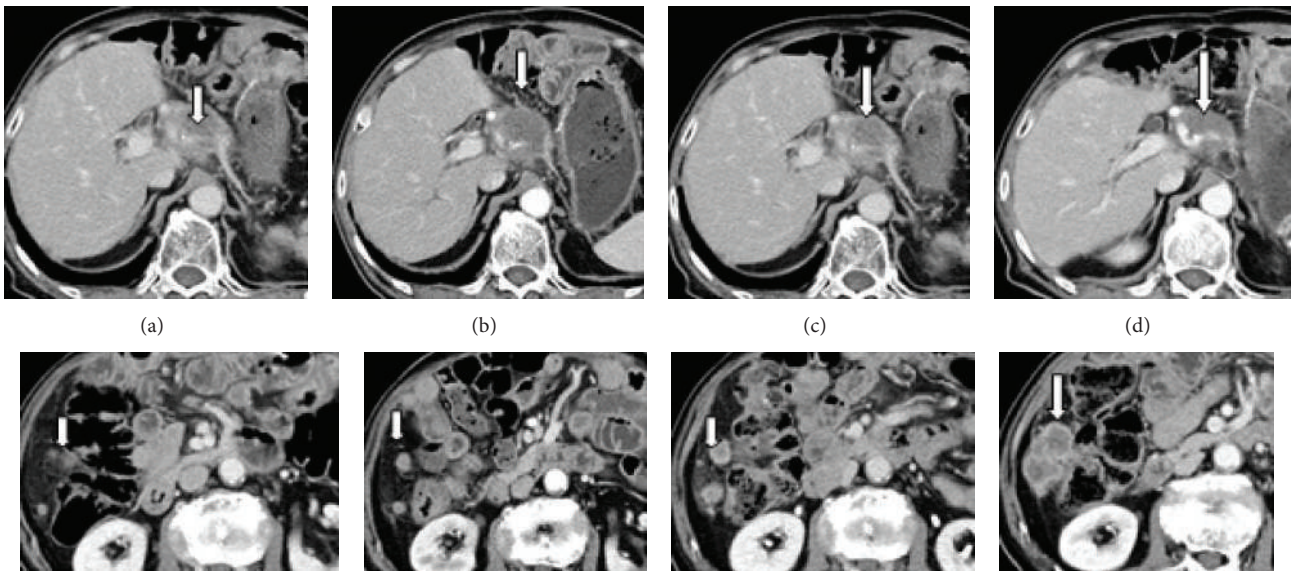
Tumor mass recurred from postovarian cancer in pelvis was regressed markedly after 12 times of oncothermia and ascites was improved and controlled by medicine.

3.12. Stomach Cancer. A 50-year-old man was diagnosed with stomach cancer (adenocarcinoma) and received operation (subtotal gastrectomy) in May 2009. Recurrent cancer has been found at anastomotic site of stomach, and obstruction of duodenum was developed in April 2012. Stent was inserted into duodenum and antrum of stomach in April 2012. Radiation therapy delivering 30 Gy in 10 fractions (once/day)



(a) (b) (c)

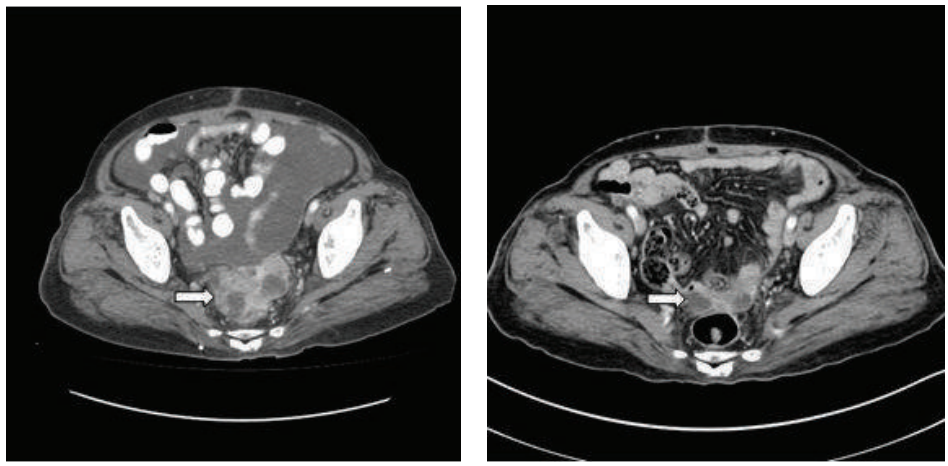
Figure 11: (a) Before OncoTx. (b) After 12 times of OncoTs. (c) Four Months after OncoTx.



(a) (b) (c) (d)

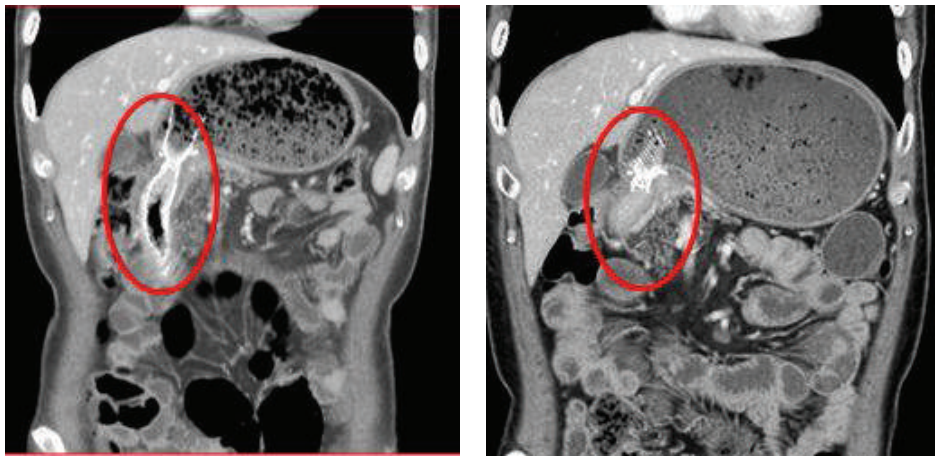
(e) (f) (g) (h)

Figure 12: (a) Before OncoTx. (b) After 12 times of OncoTx. (c) After 24 times of OncoTx. (d) After 60 times of OncoTx. (e) Before OncoTx. (f) After 12 times of OncoTx. (g) After 24 times of OncoTx. (h) After 60 times of OncoTx.



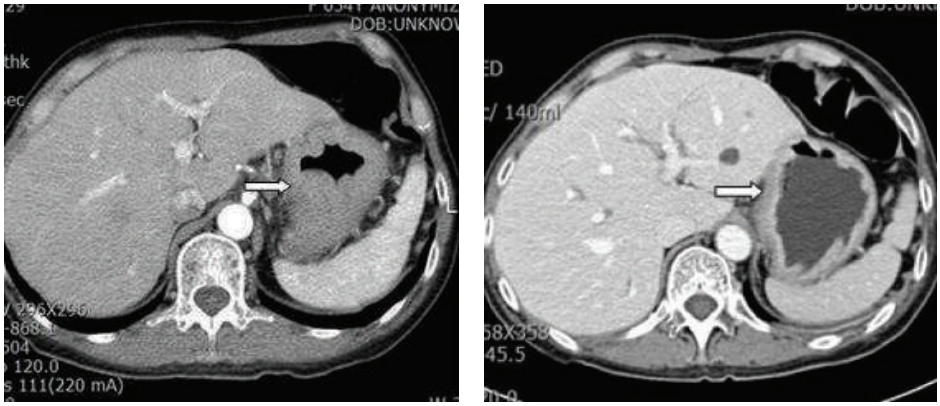
(a) (b)

Figure 13: (a) Before oncothermia. (b) One month after 12 times of oncothermia.



(a) (b)

Figure 14: (a) Before oncothermia. (b) After 12 times of oncothermia.



(a) (b)

Figure 15: (a) Before oncothermia. (b) After 36 times of oncothermia.

for 2 weeks at stent site by IMRT was given between August 23, 2012 and September 6, 2012. Oncothermia was given 12 times by 2~3 times/week between September 4, 2012 and October 20, 2012 after radiation therapy. Tumor marker CEA in serum was decreased from 5.41 (August 14, 2012) to 4.44 (October 30, 2012) (see Figure 14).

Any negative side effects did not appear even though the high temperature had been expected at the metal stent site. Metal stent in the canal or duct is not absolute contraindication for oncothermia.

Duodenal stent disappeared after oncothermia, but patient could eat food well with good food passage through duodenum. Tumor mass maybe also regressed by oncothermia.

3.13. Stomach Cancer. A 54-year-old woman has been diagnosed as stomach cancer with metastasis to the right ureter in January 2012. The patient had inoperable state and refused chemotherapy by herself. Thirty-six times (2~3 times/week) of oncothermia were given from April 17, 2012 to September 6, 2012 (see Figure 15).

Tumor mass regressed prominently in stomach, and she could eat food after 12 times of oncothermia. The total 36 times of oncothermia was given without any negative side effects.

3.14. Rectal Cancer. A 47-year-old Asian woman was diagnosed with rectal cancer and received operation in April 2010 followed by chemotherapy.

She lived well until multiple metastatic cancers were found at both lungs in January 2012. She received chemotherapy and oncothermia at the left lung for recurrent and metastatic cancer. Oncothermia was not able to be applied at both lungs because of the limitation of RF plate. Oncothermia was given 23 times (2~3 times/week) from March 30, 2012 to July 31, 2012 (see Figure 16).

Chest X-ray checked at 12 times of oncothermia revealed the regressed tumor masses at the left lung prominently, but the ones in the right lung were not reduced in size because oncothermia was not given at the right lung. CT scan was checked too. Tumor mass regressed prominently at the left lung. However those at right lung did not regress in size;

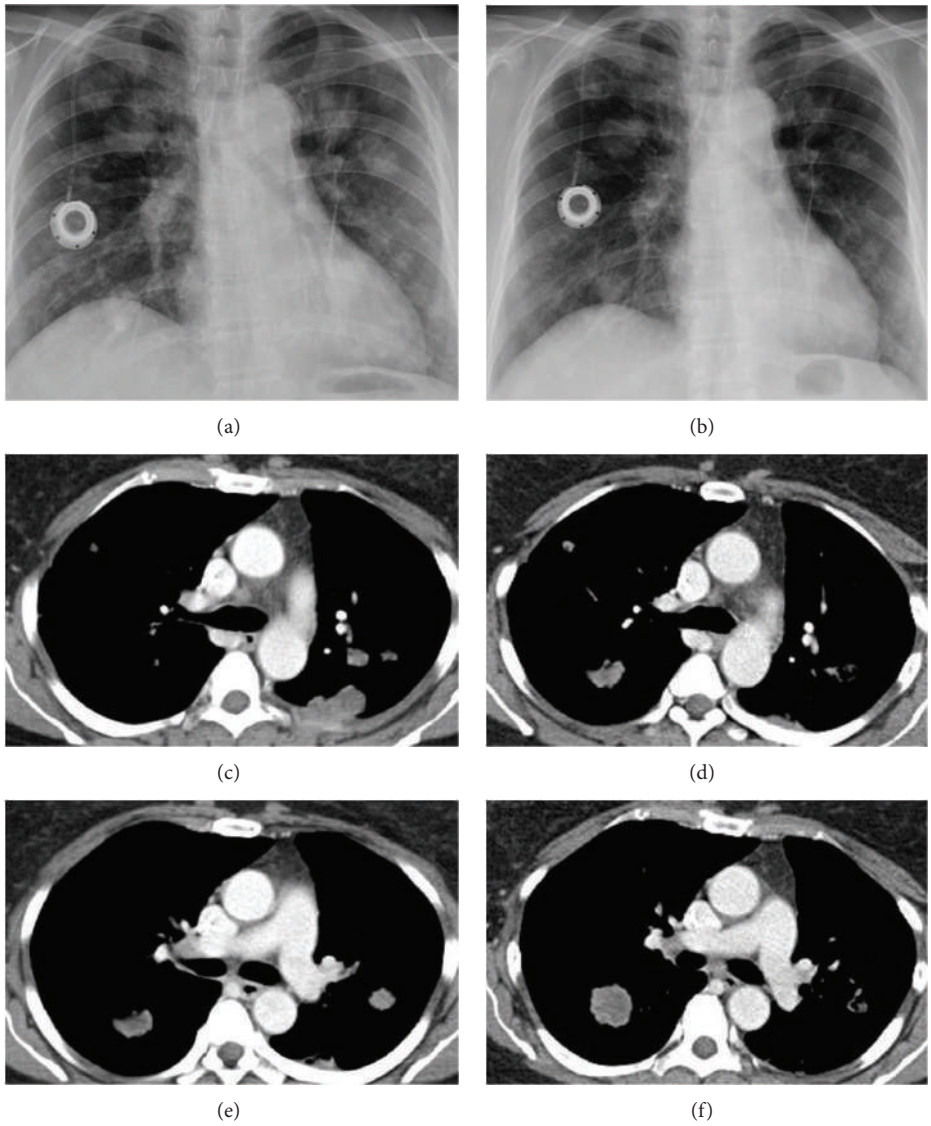


Figure 16: (a) Before OncoTx. (b) After 12 times of OncoTx. (c) Before OncoTx. (d) After 12 times of OncoTx. (e) Before OncoTx. (f) After 12 times of OncoTx.

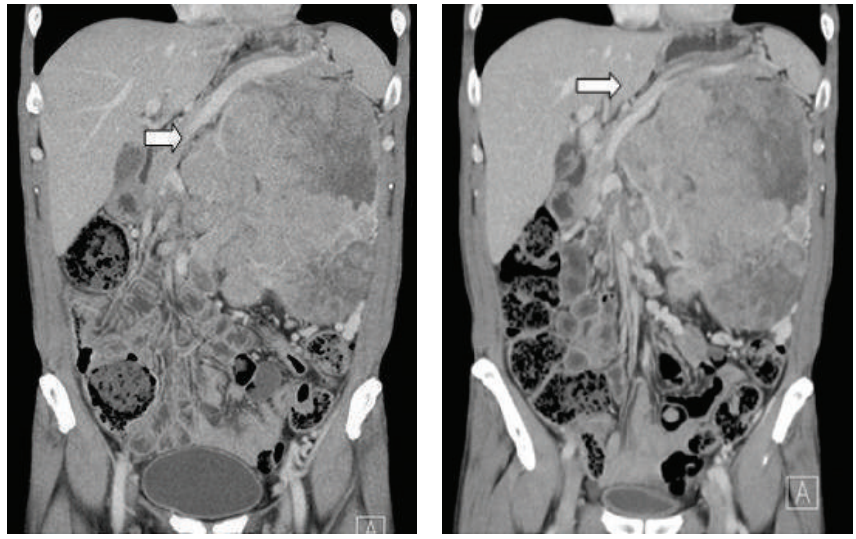
furthermore, some progressed. And the pain posterior to the left upper chest because of metastatic cancer with invasion to chest wall was also relieved after oncothermia. This case is not oncothermia monotherapy, but it must be sure in this one film that the combined chemotherapy with oncothermia is more effective certainly.

3.15. Renal Carcinoma. A 61-year-old man was diagnosed with renal cell carcinoma in January 2011. He refused to get any special treatment for cancer like chemotherapy, hormonal therapy, target therapy, operation, and radiotherapy. He received only 24 times of oncothermia (2 times/week) to tumor mass at the left upper abdomen from December 2, 2011 to February 23, 2012 for 3 months (see Figure 17).

Tumor mass did not grow during oncothermia, but tumor mass was regressed a little bit at tumor margin for 3 months. Tumor mass progressed rapidly in size and metastasized to lung prominently after 6 months from stopping oncothermia.

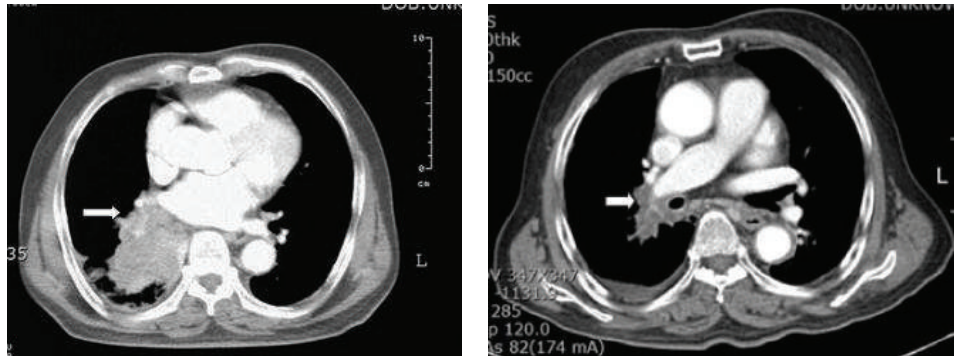
3.16. Lung. An 86-year-old man was checked by computerized tomography (CT) scan due to symptoms of the upper respiratory infection. CT scan showed a mass at the right lower lung and mediastinal area, but we could not perform biopsy because of the high risk of procedure. The patient had inoperable state and refused chemotherapy by himself. He received radiotherapy 30 Gy in 10 fractions (once/day) for 2 weeks and concurrent oncothermia 22 times (2~3 times/week) from January 27, 2012 to March 6, 2012 (see Figure 18).

Tumor regressed after 22 times of oncothermia. Combined treatment of the small amount of radiation and oncothermia revealed the prominent regression of lung mass



(a) (b)

Figure 17: (a) Before oncothermia. (b) Twenty-four times of oncothermia.



(a) (b)

Figure 18: (a) Before oncothermia. (b) After 12 times of oncothermia.

even though histologic type was not confirmed. Tumor markers of CEA 5.99 and NSE 38.97 were abnormal level in serum.

4. Conclusion

These cases together with the huge amount of other treatments answer our questions; however, of course further investigations and studies are mandatory. We had not observed oncothermia related adverse effects by dose escalation. In a negligible case, skin erythema appeared, handled with appropriate cream. It did not terminate any further treatments.

Oncothermia could be applied in very severe cases, where other treatments are dubious or inapplicable. In this situation, oncothermia could be applied as monotherapy with success. On the other hand, the complementary applications of oncothermia had no limitations for the oncothermia side of the therapy. We observed some cases which are not eligible for oncothermia, due to the mismatch of the electrodes; the bolus is not able to cover the surface smoothly. We had no contraindicated cases in our patient's spectra.

The efficacy of the treatment was depending on the number of applied sessions. The long-time applications were positive for the patients in both the curative and quality of life meanings in advanced diseases.

We observed long-time manageability of the serious stages of the cancer, making the anyway rapid fatal disease chronic, treated it longer than the anyway expected survival and the quality of life of the patients was excepted, better than in similar cases without oncothermia.

We observed feasibility and good perspectives of this method and strongly recommend making higher evidence clinical studies for stronger approval.

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