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Complete Remission of SCLC with Chemotherapy and Oncothermia (Case Report)

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Abstract

Nowadays, most oncologists have treated their patients with solid tumors by using hyperthermia with good results even though they have a large amount of different thoughts on the mechanism of oncological hyperthermia. We have treated our patients with solid tumor confirmed lung carcinoma with chemotherapy or radiotherapy with oncothermia [1] at the Department of Thoracic and Cardio-vascular Surgery at Gangnam Severance hospital since Jan, 2008. Our objective in this paper showing a case of a patient with Small Cell Lung Cancer (SCLC). The patient was and treated by chemotherapy andand oncothermia in 2008, at the Thoracic and Cardio-vascular Surgery Department, Gangnam Severance Hospital, Seoul, Korea. We report a complete remission of this patient after chemotherapy with oncothermia (2 cycles) in follow-up for 3 years.

Introduction

Hyperthermia for cancer therapy has been documented for thousands of years. [1] Conventional hyperthermia heated the surface of the body, and was supposed to achieve curative influence in the malignant tumors. Various procedures have been applied to deliver heat into the malignant tumor, e.g. hot-bath, surface heaters including heat-blanket, heat radiators etc. The aim was to change the pH- environment of the malignant tissues by the elevated temperature developed by higher rate of metabolism causing acidosis. And Hyperthermia was revived around the end of 19th Century, when the deep penetrating energy transfer was solved by electromagnetic way.

There are intensive scientific discussions about the treatment of the cancer by chemotherapy (CT) or by radiotherapy (RT) complementary with hyperthermia. [2], [3].

Although hyperthermia can have significant benefits, there are several problems to be solved.

1. Hyperthermia dosing andtreatment control is not standardized, which is a a basic challenge. While hyperthermia is the overheating of the targeted tumor tissue, the heat-dose and the method of heating tumors is not accurately defined. The blood- flow inequalities influence the developed temperature in the target, even in cases when the specific absorption rate (SAR) is homogeneous.

2. Inadequate focusing of heat and the natural temperature smearing may certainly heat up the healthy tissues around, causing definite nutrient-supply to the tumor together with increasing risk of dissemination. The misfocusing also could cause unwanted burn.

3. Heat-shock proteins (HSPs) are induced by heat-stress and the developed HSP- assisted adaptation mechanism decrease the efficacy of hyperthermia. The target can develop resistance to heat, and could become refractory for chemo- and radiation-therapies.

The description of the role of the temperature in clinical oncological hyperthermia has not concensus yet and the explanation of the heat-dose (energy absorption) dependence of the curative effects in tumor tissues is also debated, and, [4] many details have not been clarified yet. The proliferation and the metabolism of tumor tissues are more active than in their healthy counterpart, and this requests a large amount of energy consumption. Consequently, their heat production is higher than usual. Hence, the tumor tissue is usually warmer than its healthy environment. Furthermore, the additional increase of temperature by hyperthermia enforces the

tumor tissues to increase their metabolism, [5].

The temperature of the healthy tissues is regulated by the blood flow with physiological thermo-regulation. The blood flow in the healthy tissues around tumor tissues is not increased due to not increased temperature in the healthy tissues during the ideally conducted hyperthermia, till the temperature is well focused and not smeared by time, [5].The temperature increase in tumor has a supporting fact, that the thermo-regulation of the blood flow in tumor has no same physiological control, than its healthy neighborhood, [6], [7]. Consequently, there insufficient oxygen supply is available due to unchanged blood flow, the increased metabolism due to increased temperature in tumor tissues has a lack of nutrients and oxygen by constrained metabolic activity during hyperthermia. The resulting hypoxia though increased aerobic metabolism produces severe the occurred progressively acidosis and the results could be the destruction of tumor cells, [7], [8]. Furthermore, the increased metabolism decreases the ATP content of cells and therefore increased metabolism forces the cell destruction in tumor tissues, [6]. The DNA replication can be blocked also by the heat effect; the reproduction processes of DNA is slowed down in tumor tissues, [9], [10], [11].

Moreover, hyperthermia supplies the hypoxic tissues by oxygen, which increases the efficacy of radiotherapy, [12], [13].

The thermally increased metabolism enhances the reaction rate of drugs, while the increased blood perfusion supports the absorption of cytotoxins. Together with the high chemo-metabolism the drug-delivery is also high, making effective the complementary application of hyperthermia with chemotherapy. Significant pain-reduction and the few side-effects are the specific advantage of hyperthermia. These effects may contribute to considerable improvement of life quality, [14]. Hyperthermia enhances the efficiency of the immune-reactions as well, **[10]**, **[11]**; and it has primary effect to destruct the tumor cells above 42.5□, **[12]**, **[13]**.

Despite of the geart advantages of hyperthermia, it suffers a lack of acceptance, because of the controversial clinical results in practice. When the thermal effect is not adequately supplied and focused, this may increase the oxygen supply of tumor cells and activate the growth of tumors. The inappropriate focusing of heat may increase the risk of necrosis of surrounding healthy tissues and activate metastasis (cellular dissemination) of tumor cells. Also the concentration of heat shock proteins (HSP) in tumor cells is increased by the inappropriate applied heat, [15], [16]; which works against the heat-promoted processes described above.

Furthermore the developed extra HSP concentration degrades the efficacy of thermo-treatment generating a risk of heat- multi-drugs and radiation-resistances.

Unfortunately it is technically difficult to control the heat transfer reproduction and stability; furthermore there is no adequate parameter exists to detect the success and degree of hyperthermia.

Recent modulated electro-hyperthermia (oncothermia, **[1]**) is devoted to enhance the efficiency of classical hyperthermia by thermal and thermally induced but not temperature effects with the suppressing the existing disadvantages of the classical thermal treatments.

The electric field has smaller penetration depth than the magnetic one, however, its energy delivery and absoption are relatively high. The energy absorption determined by the electric parameters (dielectric constant and electric conductivity) of the targeted tissues, and also it is frequency-dependent (material dispersion). The conductivity in malignant tissues is about three times higher than that of normal tissues, [17], [18]. The higher electric conductivity is accompanied by higher dielectric constant in malignant tissues; and the extra-cellular matrix in there absorbs more energy than in the healthy areas, [19], [20]. The absorbed energy from the electric field effectively heats up the extracellular electrolyte and the temperature increases there rapidly. The cytoplasm of cell will be heated by heat diffusion through the membrane and heat diffusion acts considerably slower in the cell than the direct heat does in the extra-cellular liquid, [21]. Moreover, the suppressed warming of intracellular field reduces the non-

thermal HSP synthesis.

Tremendous heat-flow, 1500nW/μm^2, transmits through the membrane by the above mechanisms, while the natural heat-flow by metabolism, is only 20nW/μm^2. The heat-gradient in the cell allows distinct membrane currents because of its definite thermodynamic driving force. The forced current is also remarkable high: 150pA/μm^2, which is dominantly Na^+ influx into the cell. (the natural ion currents are 12pA/μm^2, sodium efflux) and the presence of these currents decreases the dynamic stability of cell membrane. In addition to the thermal flux electro-osmotic effects induce higher pressure in the cell, reaching 1.32MPa. Since malignant cells have relatively rigid membranes by their increased phospholipids concentration, the increase of the intracellular pressure distorts the cellular membranes of the malignant cells before the heat affects healthy ones, [22]. Consequently this actual pressure has a selective action to destroy the membrane of the malignant cells.

These processes allow a very important effect: the cell membrane of malignant cells is damaged before the heat reaches the cell-nuclei to synthesize HSP resisting the stress of invasion. However, membrane HSP is induced by penetratable membrane, which are supporting the apoptotic signals, to eliminate the malignant cells on the natural way.

The energy is primarily absorbed in the extra-cellular matrix by oncothermia, and penetrates into the cell by thermal diffusion through the cell membrane resulting in the damage of the cellular integrity.

Oncothermia is based on the differences between the dielectric constants, dielectric losses and on the selective absorption features of surrounding electrolyte of the cells. Malignant tumor cells are autonomic, they are not collective like their healthy counterpart. The applied frequency and its modulation is able to select the heating site on cellular basis, targeting the malignant cells individually. EHY2000 oncothermia was developed by capacitive coupling for modulated electro- hyperthermia uses a well-tuned RF (13.56MHz) electric field. Relatively little total power can be applied because of the good selectivity and well-focused heat absorption concetrates the energy on the effective way. On this way the EHY2000 regional oncothermia is for the treatment of deep-seated, organic tumors (brain, liver, kidney, lung, pancreas). This is a non-invasive, universal, easy controllable device and does has little risk of complications. Practically, there is not any complication except a few mild skin burn or burning sensation. This is one of the effective treatments in oncologic treatment field and a new modality of cancer treatment. This oncothermia is more gentle and safer than the conventional classical hyperthermia and can extend the thermal treatment efficiency to thermal and non-temperature dependent effects too. The heat dose (absorbed energy) and the applied field (electromagnetic influence) are the primary determinants of efficacy of oncothermia, [23]. It is based on a capacitively-coupled energy transfer applied at a frequency that is primarily absorbed in the extracellular matrix due to it's inability to penetrate the cell membrane, [24].

The case

The 67 years old male patient had cough and mild fever and registered in our outpatient clinic at the Department of Thoracic and Cardio-vascular Surgery at Gangnam Severance Hospital, Seoul, Korea at Aug. 10th. 2008. The chest PA and chest Computed Tomogram (CT) should about 3.6cm mass on Left Upper Lobe (LUL) with abutting to descending aorta with another small nodule in left lower lobe. Multiple enlarged lymph-nodes were seen in left hilum and left paratracheal area. We established a lung cancer, stage T3/4N2Mx. Bronchial washing cytology showed negative finding with broncho-fiberscopy, but transbronchial lung aspiration biopsy cytology revealed small cell lung carcinoma. The needle aspiration cytology showed also positive for malignancy favoring small cell lung carcinoma.

Somatometry	level
Body weight, kg	58
Height, cm	174
BMI, kg/㎡	19.16

The patient somatometry and the laboratory findings are listed in tables below:

Serum	level
WBC count, 10^3/㎕	6.27
Hb,g/㎗ - Hct,%	11.8 - 35.0
PLT count, 10^3/㎕	134
BUN, ㎎/㎗ - Cr., ㎎/㎗	17.3 - 1.1
AST, IU/L - ALT, IU/L	26 - 21
Albumin, g/㎗	3.9

The tumor markers were at Aug. 2008.

Tumor markers	level
CEA, ng/㎗	0.8
CYFRA 21-1, ng/㎗	2.3
NSE(Neuron Specific Enolase), ng/㎗	24.2

He was treated with chemotherapy Irinotecan(60 ㎎/㎡) and Cisplatin(60 ㎎/㎡) 12 cycles since Aug. 2008 to Nov. 2009 complementary with oncothermia for 1hr per session, 2 times in a week for 12 weeks (2 cycles) from Aug. 2008 to Nov. 2008. The following checks by chest PA and chest CT showed marked regression of the size of lung cancer in left upper lobe and also regression in multiple lymph-nodes in left hilum. Tumor markers at Oct. 25th. 2010 was decreased as blow.

Tumor markers	level
CYFRA 21-1, ng/㎗	2.9
NSE(Neuron Specific Enolase), ng/㎗	12.4(decreased)

He has been followed for 3 years without chemotherapy and oncothermia, having the last check-up in April 2011 at outpatient clinic. Chest PA and Chest CT showed marked regression of tumor in LUL, but residual small sized LNs in the mediastinum and left hilum were observed at Feb. 9th. 2011. However in the same time the chest PA and Chest CT showed complete regression of tumor in LUL suggesting of complete remission of SCLC.

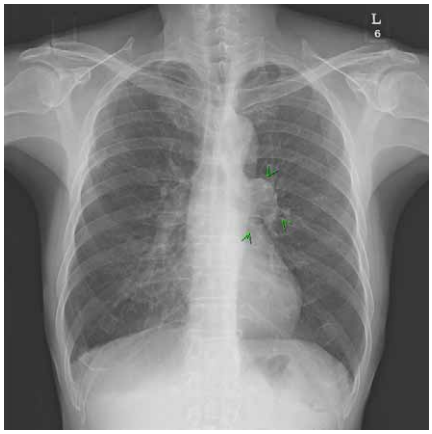


Figure 1. Chest PA showed prominent tumor at left hilum at Aug. 2009.

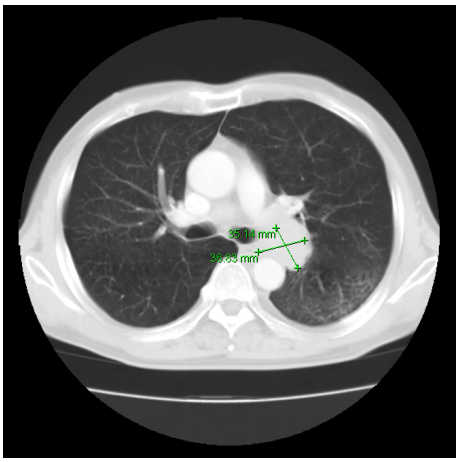


Figure 2. Chest CT showed tumor abutting to descending aorta in left hilum at Aug. 2009.

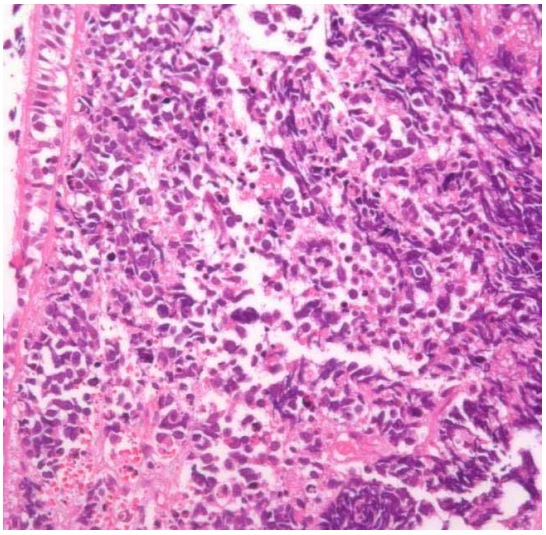
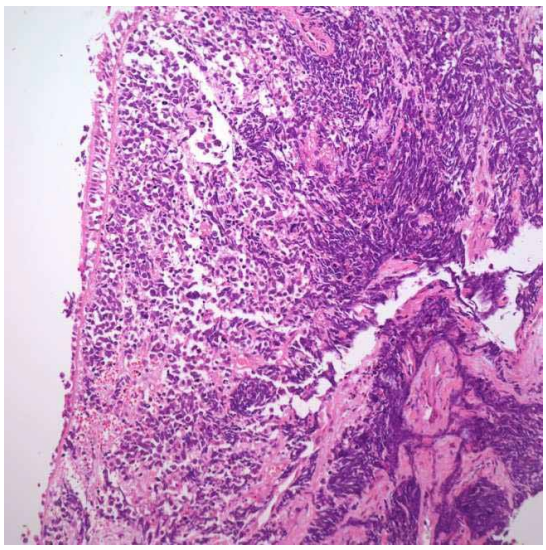
a.)  b) 

Figure 3. (a) HandE, x200; (b) HandE. x400

Subepithelial infiltration of tumor cells showing hyperchromatic nuclei, scanty amount of cytoplasm, and frequent squeezing artifact. These findings are compatible with small cell carcinoma. (HandE, x200 and x400).

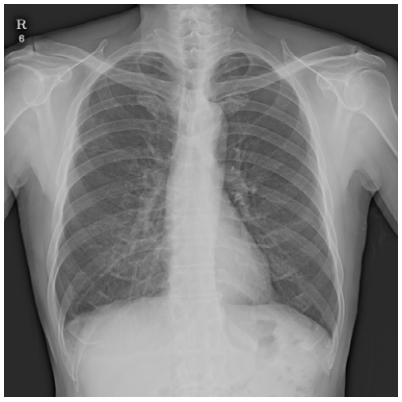


Figure 4. Chest PA showed disappearance of tumor at left hilum at Oc. 2010

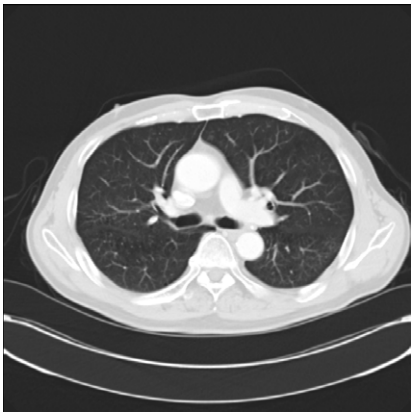


Figure 5. Chest CT showed total remission of tumor at left hilum at Oc. 2010

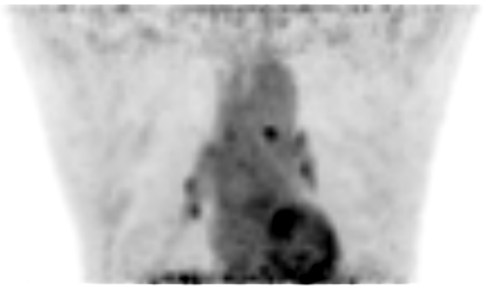


Figure 6. PET CT showed no hot uptake in the whole body at Oct. 2010

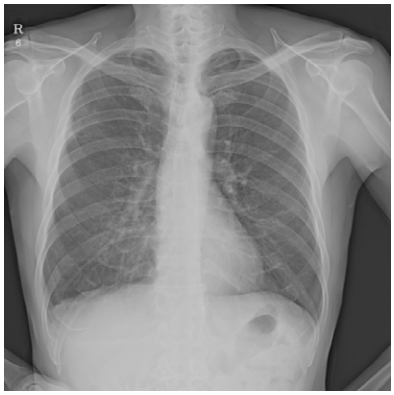


Figure 7. Chest PA showed within normal limit with no evidence of tumor at April 2011

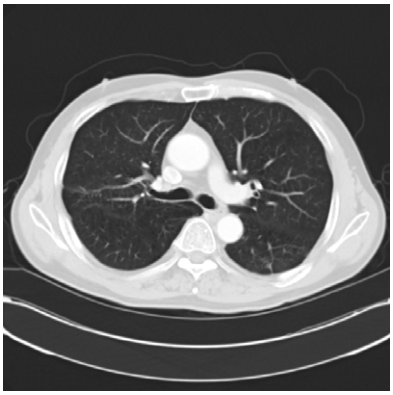


Figure 8. Chest CT showed no evidence of tumor at left hilum at April 2011

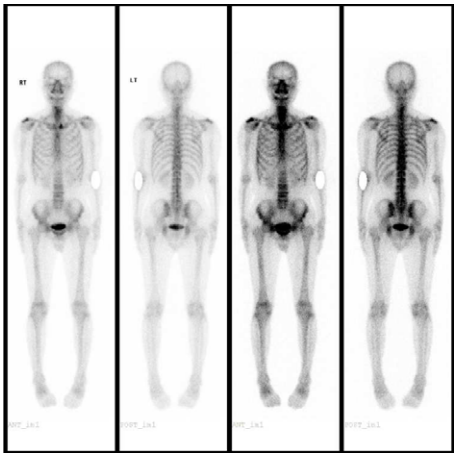


Figure 9. Whole Body Bone Scan showed no hot uptake suggesting metastatic evidences to skeletons at June 2011

Discussion

Modern lung-cancer treatment is based on platinum-containing doublets (Carboplatin and Cisplatin) and recently Gemcitabine, Taxol (Paclitaxel and Doxitaxel), Vinorelbine and Navelbine. Analysis of 52 clinical studies show the advantages of the cisplatinum based therapies (10% 1y survival increase), which reduce the risk of exitus by 27%, [27] compared to the applied supportive therapies.

The Gemcitabine-based triplets and doublets (Paclitaxel/Carboplatine/Gemcitabine; Paclitaxel/Carboplatine/Vinorelbine; Paclitaxel/Gemcitabine; Gemcitabine/Vinorelbine); had 37%, 29% 40% and 49% for one year survival and 9.6, 9.9, 8.7, 10.7 month median survival, respectively, [28]. The Gemcitabine-based doublets had better lower response rate, but longer survivals and less adverse effects.

In general, the median survival ranges between 6 and 12 months, with 7 in average. The one year survival is 24-51 %, 25-30 % in average.

Despite the well developing results, ration of the lung cancer incidence to mortality rate (0.8) is more than double of the average incidence/mortality ratio (0.3) among the <65 y population. [29]. The incidence rate of the lung cancer between the ≥65 yrs and <65 yrs old patients exceeds 14. Furthermore, lung cancer is one of the leading mortality causes for humans.

Hyperthermia (HT), combined with radiotherapy (RT) and chemotherapy (CT), seems to be a promising method enhances chemo- and radio-sensitivity and induces a high concentration of drugs within a tumor [30], [31].

However, there are some restrictions for HT in general, that hamper its use in lung cancer treatment. Namely, it could aggravate preexisting pleural liquids, as well as the lung is a complicated tissue for hyperthermia because of the permanent cooling- ventilation due to the continuous breathing.
However, some successful clinical trials had shown the feasibility of the hyperthermia method for lung cancer. Most of these are combined with radiotherapy, having 14÷70 Gy dose in the given session. The measured response rate (RR) was surprisingly high RR=75%, (n=12, [32]), and RR=100% (n=13, [33]). Others had a comparison to a control-arm (not randomized), growing the RR from RR=70% (n=30), and RR=53.8% (n=13), to RR=94.7% (n=19, [34]), and RR=76.9% (n=13, [35]), respectively. The second year survival also increased remarkably: from 15% and 15.4% to 35% and 44.4%, respectively. (The first year survival was measured as well, increasing from 30% to 55%, **[25]**).

The chemo-thermotherapy combination was also investigated for non-small-cell lung cancer (NSCLC) with success. In preclinical trials the cisplatine was shown to be effective, [36], so the clinical studies were concentrating on this drug combination. Special case report has shown the feasibility [37], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [38]. The median survival was measured in another study [39], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5y median survival was measured in another study [40], showing rather high numbers (24.5%, n=30).

One of the most advanced HT-modalities devoted to oncology is oncothermia. In the preliminary reports [41], [42], **[25]** the feasibility of the OT application was demonstrated. Oncothermia, due to the development of non-equilibrium state, is an ideal approach for the destruction of tumor cells in lung. **[25]**, **[26]**.

Oncothermia has given complete remission of malignant lsmall-cell lung cancer for more than 3 years after 2 cycles of oncothermia and chemotherapy in the Department of Thoracic and Cardio-vascular Surgery, at Gangnam Severance Hospital, YUMC, Seoul, Korea.

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