

Clinical Research on Integrative Treatment of Colon Carcinoma with Oncothermia and Clifford TCM Immune Booster

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Abstract

Nowadays oncology faces the challenge of non-toxic integrative therapies for cancer treatment. Clifford Hospital is devoted to this research and offers a full range of therapies, representing a synergy between the Traditional Chinese Medicine (TCM) and the state-of-art facilities of the Modern Western Medicine (MWM). Our present article reports research of the therapeutic efficacy and adverse reactions of integrative treatment of colon carcinoma with Oncothermia (OT) and Clifford TCM Immune Booster (CIB). The clinical study involved 157 patients in three-arms of treatments: CIB alone, OT alone and OT+ CIB combined. Results definitely prefer the combination therapy, which shows synergy of OT with CIB.

Keywords: Clifford TCM Immune Booster, Oncothermia, Traditional Chinese Medicine, randomized controlled clinical trial, colon carcinoma.

Introduction, background of the concept

The second-leading cause of cancer-related deaths in Europe and the USA is the colorectal cancer, [1]. Death from colorectal cancer is around half million in a year worldwide. The statistics has no mentionable gender differences but it is prevalent in ages over fifty. Genetic and environmental factors have definite role in development of colon-cancer, estimating 80% of the cases originated from environmental related sources, like alcoholic, low vegetable and folic acid intake, increased fat and red-meat diet and smoking habits [2].

Surgical resection remains the basic curative treatment for colon cancer, but often the patient is only partially resectable or inoperable. The prominent post-surgery prognostic factor is the stage of the disease. Patients with having no distant metastases survive more than five years by approx. 75%, while the metastatic cases show much less –five-year survival rate [3]. Metastases are dominantly start in liver from colorectal primary. Numerous kinds of adjuvant treatments are applied to prevent the potential relapse or actually invisible but developing metastatic lesions.

Chemotherapy applications

One of the oldest standard protocols for colon cancer is the adjuvant fluorouracil (5-FU) combined with leucovorin, [4], [5], [6], [7]. Irinotecan was developed for cases when the protocol of fluoracil+leucovorin was a failure [8], [9]. For comparison three different chemo-mechanisms were applied in advanced colorectal cancer cases: fluorouracil, irinotecan, and oxaliplatin; with successes, [10], [11]. Mechanism of the irinotecan and oxaliplatin are different than the elder fluorouracil, and so synergy expected, but at lest having no resistance against the treatment, [12], [13]. Until the middle of the last decade, colorectal cancer drug treatment was standardized by three active agents: 5- fluorouracil (+leucovorin), oxaliplatin, and irinotecan [14], [15], [16]. A large clinical trial was performed for 2135 unpretreated patients with advanced, poor-prognosis colorectal cancer, starting treatment with non-curative intent [17].The Kaplan-Meier survival test showed significant advantage of the combined therapies.

The disadvantages of the chemotherapies are their side effects and that the patients frequently develop multidrug resistance (MDR), which blocks the further chemo-applications. Immunotherapy is one of the non-chemical methods for colon cancer treatment. Instead of

the chemo-therapy many approaches are using antibodies and vaccines which could be highly effective in treating micro- metastatic disease [18], [19], [20].

Other strategy is the anti-angiogenic therapy which is less toxic than the conventional chemotherapies and has a lower risk of drug resistance [21], as well as could make the tumor vasculature more efficient for drug delivery increasing the efficacy of conventional therapies [22].

Complementary therapies, TCM

Parallel with the active treatments of the disease, the prevention of the colorectal cancer was investigated also very intensively [23]. The positive role of the fiber-rich diets with increased intake of Omega-3 fatty acid and high volume of fresh vegetables and fruits was suggested for individuals to prevent the colon cancer. Folic acid, Vitamin E, Selenium and Calcium intake was emphasized also.

The diets and the quality of nutrients became important, and the relation between metabolic syndrome (MetS) and its components with colorectal cancer was studied, [24]. The study supported a direct association between MetS and both colon and rectal cancers in men, but not in women.

The connection of diet and of the gastrointestinal diseases (including cancer in this track) is recognized by long time [25], [26], [27]. Some natural extracts are used in China for a long time for colorectal cancer cases, like the *Scutellaria Barbata* D.Don. The effect of this plant was shown in laboratory conditions too [28]. There are numerous publications with TCM applications for rectal and colon neoplasms; colon cancer treated by TCM was published in 124 articles in 2001, [29]. It is very interesting that the effective active agent (name Camptothecin) of chemotherapy drugs Irinotecan, Topotecan, which widely used in MWM for colorectal carcinomas, had been discovered in the old Chinese therapy by “Happy tree” (喜树), [30]. Other recipe offers for colon cancer the herbs of *oldenlandia* (60 %), *scutellaria* (15 %), *solanum* (60%), *sanguisorba* (30%), *viola* (15%), [31].

Oncologists are facing challenges to treat the patients with low toxicity, high quality of life and long survival time. They are looking for solutions in anticancer drugs in Chinese herbal medicine. Clinical data showed anticancer properties of some herbs [32], [33], [34]. Even the palliative and post- treatment care has herbal medicine with success [35].

The ancient philosophy of TCM has definite similarities of the novel hypotheses of integrative medicine, where the whole body in its integrity and the general overall complex system is studied, rather than the body-parts or individual processes in the system. The basis of theories of TCM leading to syndrome differentiation and examples of the corresponding treatment strategies are comparable in general with the evidence based medicine preferred by MWM, as shown in the Table 1. [30].

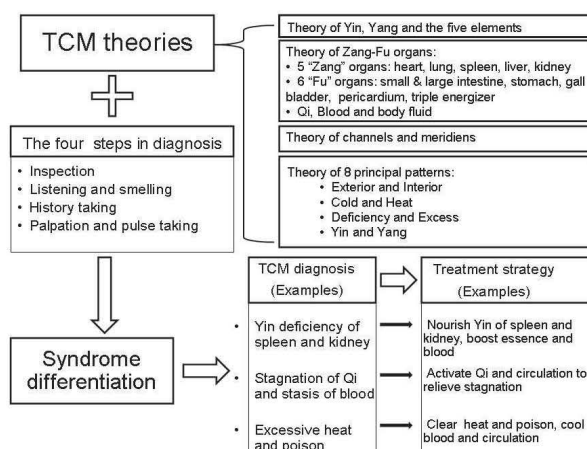


Table 1. The structure of TCM theories [30]

The body is in homeostasis in normal healthy state. TCM is directly based on the general and overall homeostatic control of the human body. The homeostasis created by multiple negative feedback processes, keeping the actual state apparently constant. Each negative feedback can be described by a balance of the apparently controversial effects, a “dynamic overlay of opposing forces” [36], which is the basic of the dialectic philosophy. This was formulated by the ancient Chinese philosophy (Lao Tzu “The Old Master” [37], [38]), and approximately in the same time in Western (Greek) philosophy (Heraclitus of Ephesus, [39]) as well. Later Hegel had synergized the dialectics, [40], formulating the thesis-antithesis-synthesis unity behind of the dynamic movements. The dialectical points are considered also in the roots of medical thinking, [41]. The numerous well controlled negative feedback loops, keep the actual state definitely “constant” despite of its energetically open status. The disease breaks up the relative equilibrium, and the body tries to reestablish the homeostasis by forced natural feedback mechanisms.

When recognizing the disease, we can act to help the natural feedback loops (this is the aim of the TCM) or we can influence independently, operating outside constrains intending to modify the actually recognized local disturbances. This action is typical in MWM, when the wide range medical knowledge concentrates on the details of the body-parts, ignoring in some cases the interconnections and integrity of the body as a complex system. (Typical behavior of the complex system, that it is more than the simple addition of their parts.) MWM works against the natural homeostasis on this way in many cases. The constrained action induces new negative feedbacks from the natural physiologic control, to reestablish the homeostatic. The body integrity starts to fight against our constraints too, forcing the natural processes exposing it to cross-fire by the disease and the independent medical action. This controversial situation happens with classical hyperthermia, when the constrained massive temperature change is physiologically down-regulated (or at least the physiology works against it by the systemic [like blood-flow] and local [like HSP] reactions). The natural therapy must help the body’s internal corrective actions to reestablish the healthy state.

The present study applied ‘Clifford TCM Immune Booster, which is a well defined and carefully prepared mixture of TCM herbs. Main constituents are: Rhizoma Smilacis Blabrae, Radix Angelicae Sinensis, Rhizoma Atractylodis Macrocephalae, together with multiple minor additions mixed in the tincture.

Classical hyperthermia applications

Of course the independent constrains are necessary want the natural processes are too weak to make corrections or somehow entirely blocked in the actual disease, but the effect always has to consider the effects of disturbances in the entire system. This is the problem of the

unlimited force of hyperthermia, when the body tries to correct the increasing temperature, increasing multiple physiological answers trying to correct the shifted temperature. In this applications of hyperthermia starts a competition between the processes, and became difficult keeping the entire action under control. Anyway the forced local temperature increase offers many advantages for gastrointestinal track, [42]. The response rates of early treatments were remarkable, they were over 50% [43], [44], [45], [46], [47]. Certain palliative effect for pain was also observed in these applications, the pain was certainly reduced by 78%; 56%, [46]; 86%, [45]; 79%, [42]; for 32, 34, 48 and 69 patients involved in the study, respectively.

Recurrent, locally advanced colorectal cancer was studied by hyperthermia adjuvant added to standard radiotherapy protocol [48], [49]. The objective response rate was 54% with combined therapy while the radiotherapy alone reached only 36%. In recent studies, results on unresectable or locally recurrent, advanced colorectal tumors were studied with extreme surface cooling facilities, avoiding the surface burn, [50]. The median survival times were 24.3 and 17.1 months in combined and sole radiotherapy groups, respectively. Other study with the radiotherapy combined with capacitive hyperthermia for recurrent or nonresectable colorectal tumors had only two cases progressive disease from n=44 patients. [51]. Similar results were obtained with other studies [52], [53], [54] as well. Comparison [53] the active group (n=35) to a control one (n=36) had shown clear advantage of hyperthermia. Success could be obtained by hyperthermia applied together with chemotherapy in case of preradiated treatments [55]. In recent studies in combination with chemotherapy, the response rate of the treatment of refractory colorectal cancer as 2nd line treatment by 5FU/LV with the addition of Irinotecan is 22% and leads to a progression free survival of 6.3 months [56]. In combination with hyperthermia [57] the objective response rate was 33%, while the median time to progression was 8 months (1-28 months) and the median overall survival was 12 months (2-28 months). This hyperthermia study ([57]) concluded that hyperthermia does not increase the toxicity of the 5FU/LV/Irinotecan therapy, and indicates benefits form the combined treatment.

Application of hyperthermia was introduced preoperatively as well, [58]. Comparing the postoperative results [59], in case of tumors invading beyond the muscularis propria the overall survival was 86.5 and 50.9 months for with and without hyperthermia treatments, respectively. In cases of the lymph- node metastases the results were 92.5 vs. 51.7 months for with vs. without, respectively. Other, phaseII investigation of locally advanced rectal cancer [60] supported the feasibility of preoperative hyperthermia. The preoperative hyperthermia applications were also successful in trimodal (chemotherapy, radiotherapy and hyperthermia combination) approach, [61], [62] even when it was applied intraoperatively [63].

Oncothermia applications

The problem of the malignant diseases is clear: these diseases are systemic, their appearance is local, but it is illusory to treat it only locally. This systemic effect manifests itself in the dissemination of the cells from the original (primary) tumor, and in a second step the malignant cells travel in this way far away from their original place, and could clog in sensitive organs, like brain, lung, liver; forming lethal metastases. The disseminated cells attacking the organs which are crucial for life, form new tumors (metastases) in these organs, and this is the main danger of malignant tumors. (the benign tumors are really local, they are growing in the local volume, but no dissemination and no metastasis forming happen in these cases.) The heavy life-threatening effect of metastases has been observed on statistical basis on colorectal adenocarcinoma collecting data for 15 years [64]. When no metastases were present, the long-term (10 years) survival was around 90%; while was 60% in case of regional metastases and only 15% when distant metastases were developed by the patient.

The dissemination of the malignant cells is the consequence of the certain autonomy of the cells, which lost their cooperative control, escaped from the homeostatic harmony of the tissue organization. The tumor is a set of the autonomic cells, which are not connected to others for information exchange, and supporting each other, even oppositely, they are “individual fighters” to keep themselves alive in a hostile environment of the other malignant cells and the possible attacks of the overall controller the immune system. Physiologically the crucial point is the loosing communication between the cells, which is responsible not only for the lost “harmony” with the system but also blocs the availability to give natural outer signals for apoptosis and in the dissemination point of view, the lost connections made the cells freely movable. The autonomic, aggressively metabolizing and dividing cells are seeking for large amount of nutrients and oxygen, which are delivered by the blood-stream, so the dissemination of the independent cells into the blood-vessels is a natural consequences of their freedom.

Oncothermia had formulated a new paradigm [65]; it answers positively on the doubts above. It radically reforms the hyperthermic oncology, introducing new technology for selection of the target- tumor, for principles of its elimination, and for the dose concept controlling the therapy.

The targeting in oncothermia based on the microscopic energy-delivery, heating up the extracellular electrolyte in the immediate vicinity of the malignant cells instead of the artificially focusing on the full volume of the tumor. This controlled effect makes possible to concentrate the absorbed energy on the task, and not increase the temperature where it is not necessary. The biological basis of the selection is the high glucose flux consumption of the malignant cells compared to their healthy counterpart. (This difference is the basic of the positron emission tomography [PET] as well.) The higher ionic concentration of the extracellular electrolyte as well as the disordered structure forming by the autonomic malignant cells makes possible to distinguish these cells directly by their electromagnetic (impedance) properties to attack and kill them [66]. This controlled micro heating makes possible to introduce the dose as the absorbed power [67], [68]; like it is used in the standard radio-therapy as well. The physiological feedback loops to correct the higher local temperature and the constrained effects of local heating are hindered by oncothermia, and the energy of the electric field became a synergetic partner of the microscopic temperature increase [69]. This makes possible the oncothermia applications in wide range of malignant diseases [70], and introduces it [71] as the fourth column of the gold-standard oncological methods, additional to the surgery, radio- and chemo-therapies.

Oncothermia activates the natural processes to block the dissemination; it reestablishes the cellular connections between the malignant cells. Two kinds of such bonding connections are important between the cells among normal conditions: the adherent connections exchanging signals from neighboring cells, and the junctions (gap-junction, tight junction) allowing molecular exchanges between the cells. These connections represent mechanical/chemical bonds, which are limiting the cellular freedom to disseminate, avoiding their motility due to the lazy connections to the tumor mass. Oncothermia is able to reestablish both kind of connections (adherent- and junction-types) and with this blocks the number one life-threatening danger: the dissemination, [72]. The built up connections could force not only the sticking together, but make bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells. The cells are able to make some-kind of harmonic cooperation again, and one of its consequences is the apoptotic cellular death. This kind of cellular life-regulation has additional benefit too: elimination of the cells does not liberates toxic materials and does not induce consequent inflammation in the tumor region. The inflammatory tumors have generally worst prognosis than the non-inflammatory ones, so oncothermia improves the life prognosis, helping the complex process of the longer survival

with better quality of life.

On the technical point of view, the reestablished connections between the cells rearrange the current distribution inside the tumor, developing a positive feedback mechanism to destroy the malignant cells on natural way.

One of the definite possibility to fight against the cancer diseases is to recognize the tumor as early as possible, to avoid the dissemination and metastases, and start the treatments as early as possible. Unfortunately, most of the patients are starting their oncothermia sessions, when the malignant cells already invaded into the blood-system. The blood-transported cells can be blocked easily by the brain, lung, kidney, liver, etc., as consequence of this process, and most of the patients starting to be included to oncothermia treatments, have distant metastases, which more likely causes fatality, shortens the overall survival time and badly affects the quality of life of the patients. This situation is a major challenge of the oncothermia treatments.

Oncothermia picks-up the gloves, and makes research to eliminate the distant metastases too. One of the main challenge to treat metastatic lesions in general is the diagnosis, recognizing where the metastases are present. Oncothermia is basically a local treatment. Of course, when the metastatic tumor is recognized its treatment is simple, make it on the same way, as we do in case of primary tumors. However this is not enough in most of the cases. The disseminated cells forming various metastases, which are actually too small to detect, but their presence makes definite suppress of the life-span and the quality of life. In consequence, the task is to act systemically with the local treatment. It looks impossible, but studying the systemic behavior of the malignant effects (which acts systemically form a local source), the action is not impossible. According to our common knowledge the local therapy of radiation is not available in cancer patients with multiple metastatic lesions. However, one of the interesting, and so far not completely understood processes, is the systemic effect of the local treatments in radiotherapies, the so called abscopal (out of the target) or bystander effect. The first published observation on systemic effect of local radiotherapy was made by R.H. Mole, who proposed the term “abscopal effect” in 1953 [73]. This phenomenon shows a systemic effect only by local treating. Effect was observed [74] outside the treated field of ionizing radiation [75], but it is generally under-recognized in the clinical practice [74]. It is originally defined as the systemic effect of radiation therapy observed in distant tumors from the site of irradiation field. It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also [76]. Sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy [77]. These complementary applications have recently received attention as new therapeutic facility [78]. The possible effect of pulsed electric field and radiotherapy on abscopal process was studied, [79], so our studies targeting this process, replacing the radiotherapy with oncothermia. The effect was shown in mice experiments [80]. Oncothermia was able to produce the same effect, controlled by the local tumor-treatment on the untreated distant other tumor in mice model, (HT29 human colorectal adenocarcinoma xenograft). A strong abscopal effect was observed, when sterile inflammation (E. coli LPS) as immune-stimulator was applied [81].

The effect makes promising facility for the future oncothermia applications. There was a human case of abscopal effect observed in a patient with multiple metastatic non-small-cell lung cancer. Patient was treated with fractional radiotherapy accompanied with oncothermia and granulocyte-colony stimulating factor (GM-CSF). The result [82] is amazing and clearly shows the future dictions of the oncothermia research.

Oncothermia has new facilities to treat advanced, heavily pre-treated (failed pre-treatments), colorectal cancer. A study was performed, [83], including n=218 patients. Patients were

categorized for rectum (n=92) for colon (n=114) and for rectosigmoid junction (sigma, n=12) carcinomas.

The median survival time is 28.5m (mean 34.4m), while the median time from the start of oncothermia therapy was 8.6m (mean: 14.8m). Oncothermia was applied weekly 2-3 times 6-12 treatments with 20 cm diameter electrodes. First year survival rate for oncothermia was 84.9%, (In comparison the SEER and Eurocare data are 72.0% and 68.9%, respectively.) The median of colon, rectum and sigma cohorts are 25.6m, 27.4m and 28.0m, respectively. The parametric decomposition shows medians 59.5m and 21.4m for responders and for non-responders in case of colon, and 54.3m and 22.6m for responders and for non-responders in case of rectum, respectively, Ratio of responders by the parametric decomposition were 44.2% and 57.1% for colon and rectum, respectively.

Studies were performed for the most common distant metastases of colorectal primary neoplasm: the secondary malignancy in the liver. A study was devoted to see the preoperative application of oncothermia for liver metastases from rectum carcinoma [84]. The primer-tumors were inoperable (R2). A trimodal therapy was applied: radiotherapy: 45+5 Gy, (fractional), chemotherapy: 5- FU/Mitomycin-C (2x), Oncothermia: 60 min, diam.30 cm (8-10x), Result: after oncothermia all patients become eligible for operation. The results of operation was: 71% of patients were in condition for complete resection (R0) while one was partially resected (R1) and one was not successfully operated, (remained R2).

One of the earliest study of oncothermia on colorectal metastases to liver (n=80) was published in 1999, [85]. The median survival was significantly higher with oncothermia than expected without this treatment. The overall median survival was expected as 11 months, while for the multidrug resistant, refractory patients where oncothermia was applied alone, the median survival time was 24.4 month, while for the patients eligible for resensitizing a chemotherapy and oncothermia applied as complementary, the median survival time was 21.5 month. Other study of advanced metastatic liver form colon was shown at ASCO [86]. The local clinical response of liver metastases was 28%; the quality of life reported better for 50% of the patients.

Other study is devoted to compare of first-line (without oncothermia) and second-line (with oncothermia) therapies for colorectal cancer liver metastasis (n=15) [87]. The local response after the second line was significantly better than after the first one, without extra toxicity for the patients. The median survival was 23 months, while the historical expectation: 10-20 months. Tumor-progression was observed mainly outside the applied electromagnetic field.

A first-line, phase II. study (n=30) was devoted to compare the effect of platinum derivatives of liver metastases from colorectal cancer origin, [88]. The median survival time was 22m, (10-34), while the median relapse-time was 9m (6-18). All the platinum-derivatives show 20% response rate and 50% improving the quality of life (KPS). The main side effect was the anxiety reduction (83% of the patients), the nausea, vomiting was 13.3% while the other side effects were under 10%. Definite oncothermia side effect (erythematic + mild adipose burn) was observed in 6.7%. Independent study of Oxalyplatin +oncothermia (n=12) and of Cisplatin + oncothermia (n=18) shows definite differences. The local response rate was definitely higher for Cisplatin, while the other benefits shows significantly lower results, the side effects differs also significantly.

This study was made for advanced, non-operable rectal carcinoma (n=65) and its liver metastases (n=29), [89]. Oncothermia was applied by 2-3x / week with concomitant chemo- and radiotherapy. Overall local clinical response (CR+PR+SD) was 96% for rectal primary and 86% for liver metastases.

Methods

TCM and MWM were combined to treat patients with advanced colon cancer. The principles used to treat cancer include eliminating toxins and pathogens, boosting immune system and enhancing their nutrition by CIB method, [90]. These therapies are non-invasive, non-toxic, safe, and effective; utilized in ways to support and enhance the effects of each other, while minimizing their deficiencies. The therapeutic protocol was the combination of oncothermia with Clifford TCM Immune Boosting (CIB) method.

Oncothermia was applied 3 times a week, 60 min/session, 20 cm electrode. The applied forwarded power was 100-150 W, depending on the personal tolerance of the patient. 15 sessions in a cycle, 7-10 days break between cycles. Oncothermia was not applied in female menstruation period.

The protocol of the Clifford TCM Immune Boosting (CIB) [91] was applied per os. It was administered one dose per day (divided into two equal portions), in 200ml portions. One portion, bid. (morning and night, after meal).

Standard oncothermia was applied in primary and secondary lesions (see Figure 1.)



Figure 1. A typical arrangement of oncothermia treatment for liver metastases from colon primary

The study was phase II, randomized, single-blind, controlled, having three comparable arms to measure the efficacy. For objective single-blind method individuals did not know which group they were in. In order to avoid bias, trial operators and therapeutic effect evaluation personnel were not the same members of the staff.

The three groups of patients were:

- Croup A (treatment): 51 cases Oncothermia in combination with Clifford TCM Immune Booster
- Croup B (control): 50 cases mono Oncothermia
- Croup C (control): 53 cases mono Clifford TCM Immune Booster

Their inclusion criteria were:

1. Confirmed colon carcinoma diagnosis
2. Not suitable for surgery (inoperable cases) or patient refused surgery (personal not-eligibility)
3. Recurrence after surgery or carcinoma was not completely resected
4. Predicted survival time > 6 months
5. Score of Karnofsky Performance Status (KPS) > 50

The exclusion criteria:

1. Surgical intervention < 3 weeks
2. Incomplete healing of wound in Oncothermia treatment area
3. With active bleeding, or local blood circulation occlusion in treatment area
4. With emotional disturbance, personal refuse
5. Oncothermia arrangement cannot fit to the treatment area due to individual physical variation
6. Patient had metallic implants or replacements, or any electronic device in the treatment area

The logistics of the treatment protocol (see Figure 2.) was applied for N=154 patients, satisfied the criteria of the study. The final evaluation of the study was after two-years follow-up period, when statistically were evaluated

1. the efficacy of the therapy,
2. the quality of life
3. the survival data

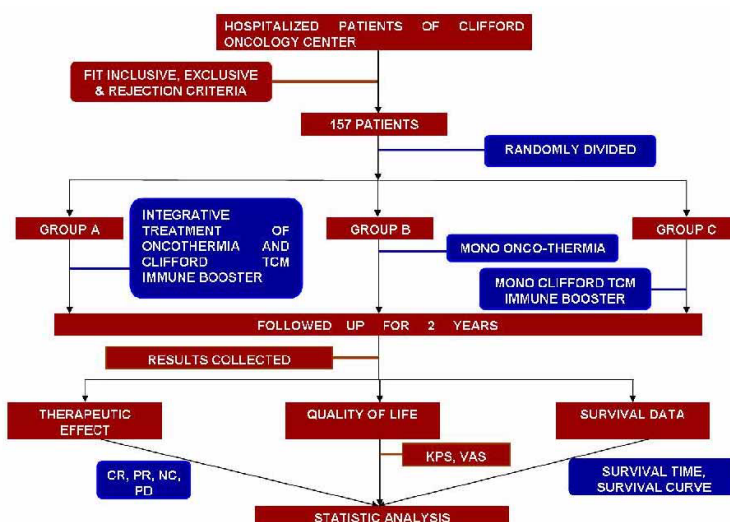


Figure 2. The randomization and logistics of the treatment protocol

The statistical evaluation was based on $\alpha=0.05$ (CI=95%). Non-parametric survival analysis (Kaplan- Meier Plot) was applied together with:

- Ranks sum test
- t test and multiple factor variance analysis
- χ^2 test

Results

Case report

A typical successful case-report shows the process.

- Male patient, 80 year old, diagnosed with ulcerative transverse colon with moderately differentiated tubular adenocarcinoma of stage IV (T3N1M1, with lung metastasis) in April, 2008 (see Figure 3/a.)
- Radical resection of colon cancer was performed in May, 2008
- Came to Clifford Hospital for non-toxic integrative treatments for cancer after surgery

- Treated with Oncothermia in combination with Clifford TCM Immune Booster
- Along with the integrative treatments of chelation, medical ozone, acupuncture, nutritional therapy, Qigong, Taiji, etc

Patient was rechecked on March 23rd, 2010 (see Figure 3/b.):

- No relapse, no metastasis, good nutritional state, KPS 90, VAS 0~1, increase in body weight: 12 kg since surgery
- Normal blood routine and tumor markers results

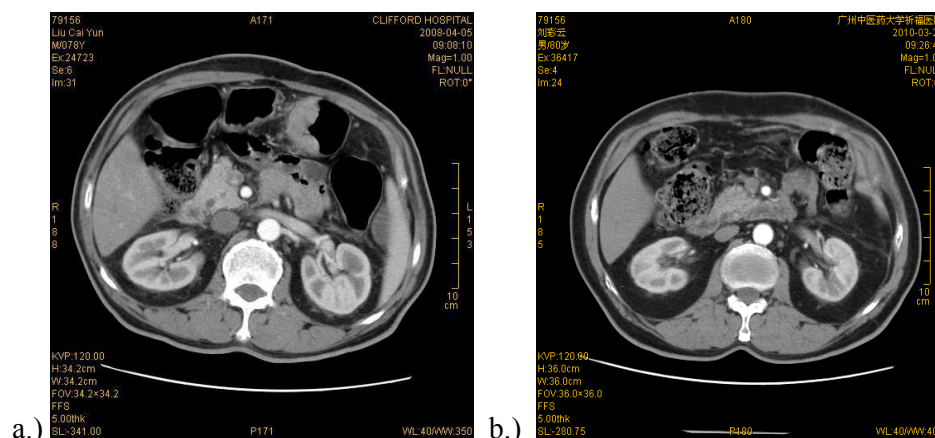


Figure 3. (a) before treatment, April, 2008; (b) after treatment, March, 2010

Therapeutic effects – local responses

The local clinical control and response was carefully measured according to the international standards, [92]. The distribution of the local clinical response by its efficacy is shown on Figure 4. The majority of the success in CR and PR categories were detected in the group A, where the complex treatment was applied.

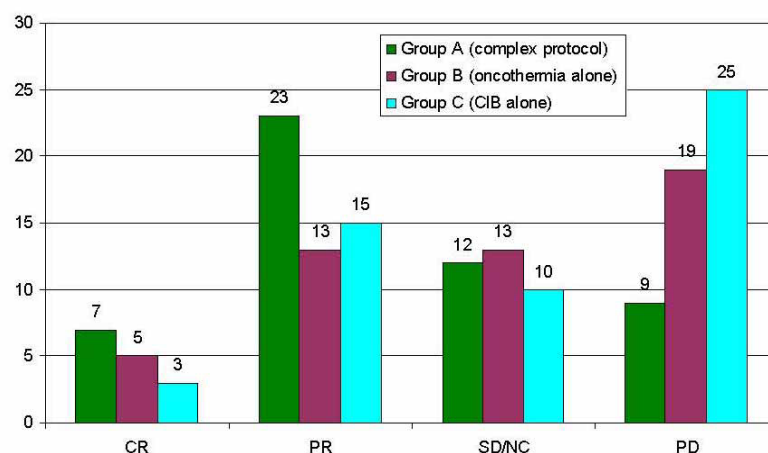


Figure 4. Local response of the patients involved in the study in all the groups. The number of patients are displayed

The grouping by the study-arms (see Figure 5.) shows a growth of the in-efficient categories in groups B & C, while in group A the vast majority of the results is partial remission, and less than 20% remained in progressive tumor-growth.

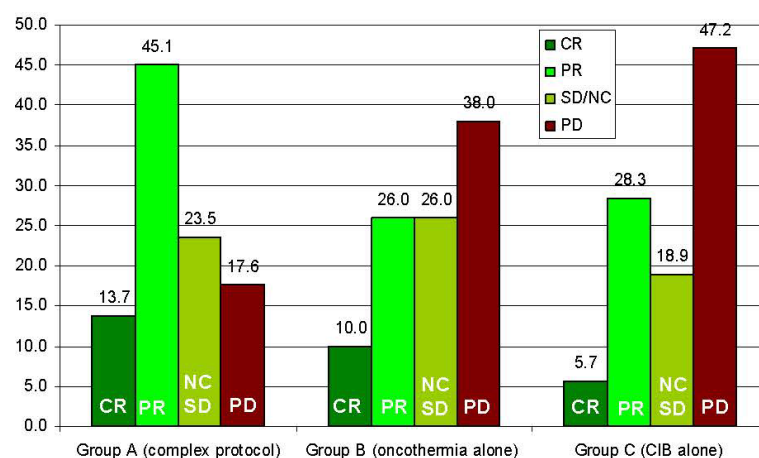


Figure 5. Efficacy of the local response by study-arms. There the percentages are shown by groups

The improvement (shrinking of tumors) produced by the treatment (CR+PR) is shown by arms and by improvement categories, (see Figure 6.). The no-change (NC) in the advanced stages like in the cases of the patients involved in the study is the result of stabile disease (SD), also a kind of response, the further growth of tumor had been stopped. The overall response in this meaning (CR+PR+NC/SD) is shown in Figure 7.

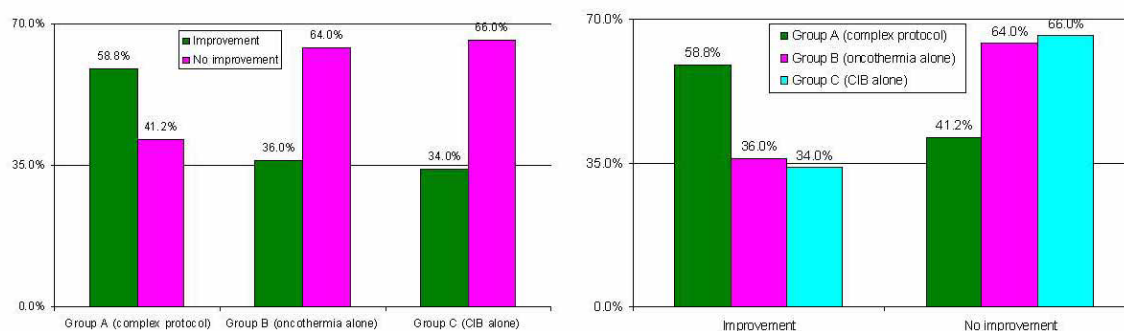


Figure 6. The improvement by the various treatments (Values are in percentages)

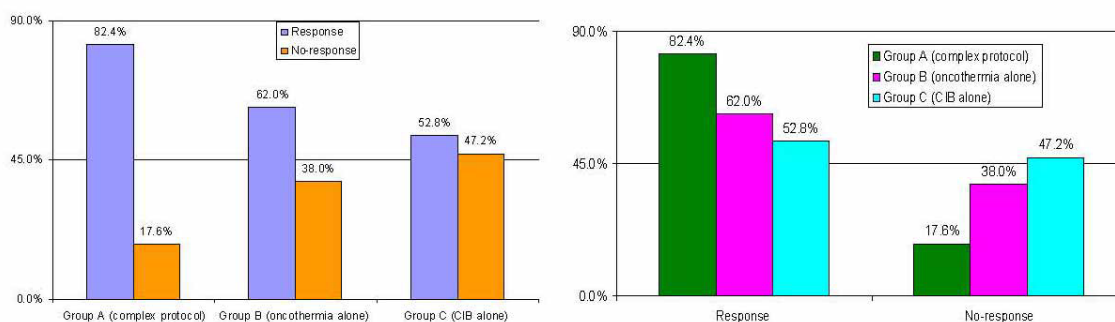


Figure 7. The overall response by the various treatments (Values are in percentages)

Therapeutic effects – survival time

The survival time was measured by non-parametric distribution evaluation (Kaplan-Meier plot, [93], see Figure 8.).

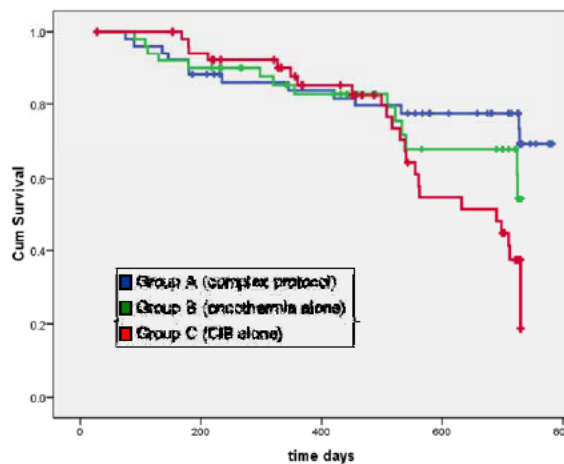


Figure 8. Kaplan-Meier plot of the survivals

Therapeutic effects – quality of life

The quality of life was measured partly with Karnofsky Performance Score status, (KPS, [94], [95]; partly with Visual Analogue Scale VAS [96]).

KPS is an assessment tool intended to assist clinicians and caretakers in gauging a patient's functional status and ability to carry out activities of daily living. The three arms of the study shows that the Group A (complex treatment) has definitely different distribution than its counterparts B & C, (see Figure 9.)

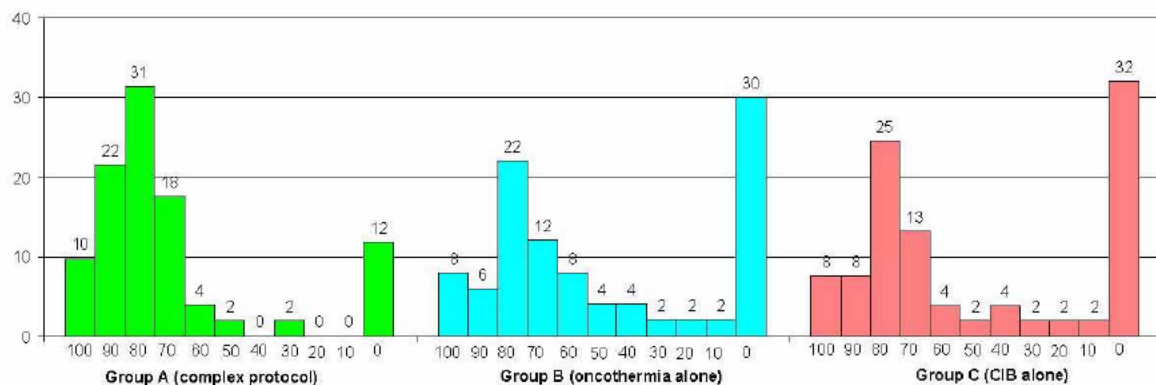


Figure 9. The KPS grouped by study-arms

Describing the major categories, three groups of KPS can be formed, as shown Table 2. According to this categorization the patients' quality of life is shown by study-arms (see Figure 10.) and by KPS grouping (see Figure 11.).

Able to carry on normal activity and to work; no special care needed (KPS=80-100)
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed (KPS=50-70)
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly (KPS=0-40)

Table 2. Major groups of KPS

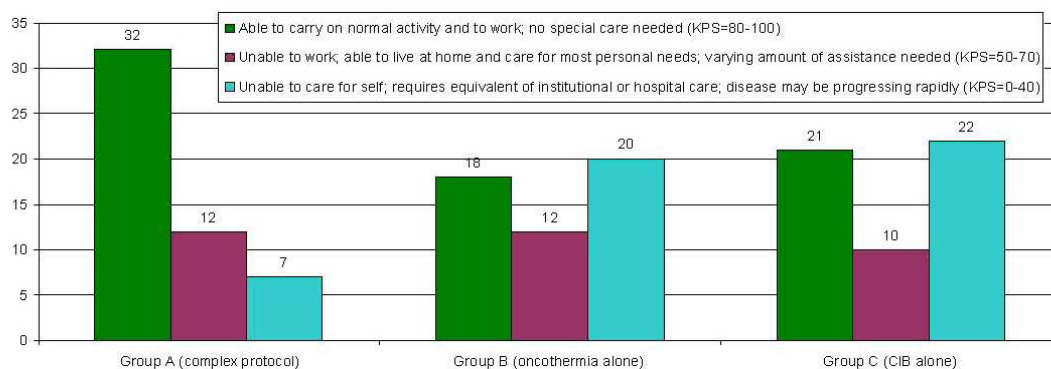


Figure 10. KPS grouped by study-arms

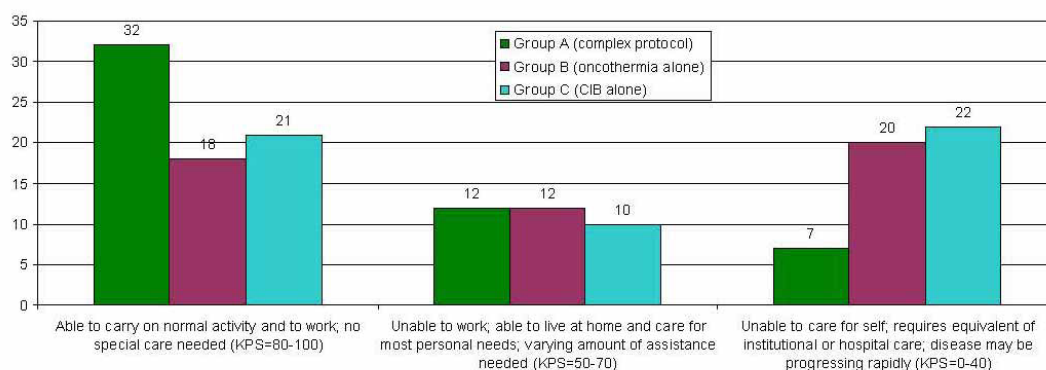


Figure 11. KPS grouped by major categories of quality of life

VAS score measures mainly the pain-effect as a decisional factor of the quality of life for cancer patients. This important quality factor is shown for all the patients in Figure 12. The VAS score grouped by main VAS categories (see Figure 13.) and by study-arms (see Figure 14.) shows definite differences favouring the group A again.

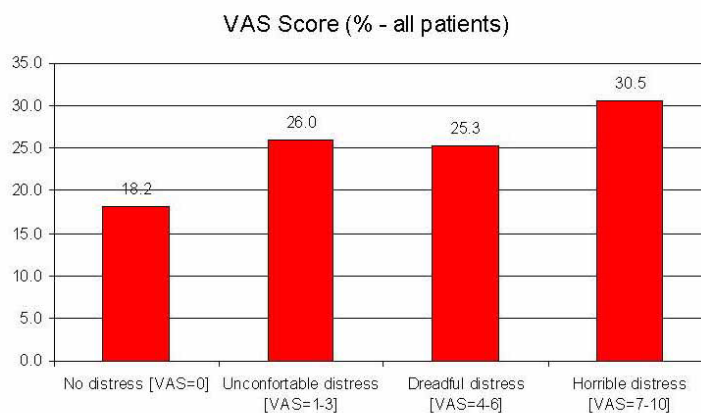


Figure 12. Overall VAS score after the full therapy regime of all the patients involved in the study (values are in percentages)

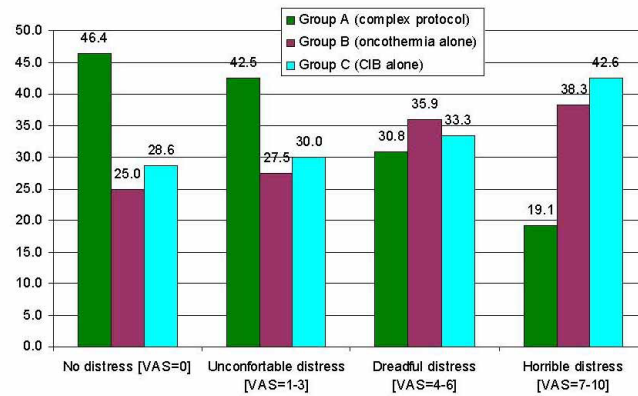


Figure 13. VAS score grouped by main VAS categories (values are in percentages)

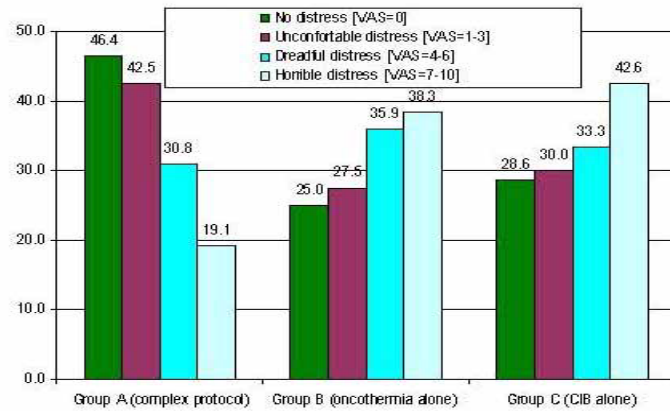


Figure 14. VAS score grouped by the study-arms (values are in percentages)

The data of the statistical evaluation are shown in Table 3. and Table 4.

Rank Sum Test on KPS of 3 Groups			
	<i>u</i>	<i>P</i>	
Group A and Group B	-3.0906	0.002	<0.05
Group A and Group C	-2.9906	0.0028	<0.05
Group B and Group C	-0.0133	0.9894	>0.05

Table 3. Rank-sum test for group-pairs

Rank Sum Test Results on Every Two Groups		
Groups	<i>P</i>	
Group A and Group B	0.0204	<0.0500
Group A and Group C	0.0362	<0.0500
Group B and Group C	0.9392	>0.0500

Table 4. Rank-sum test results for group-pairs

Adverse reactions of oncothermia in treatment are was some solitary fat-burn in adipose regions in the treatment area. Temporarily slight erythematic spot and slight pain could happen. No other toxicity was observed.

Discussion

Results are showing significant synergy of oncothermia and Clifford TCM Immune Boosting (CIB) method. The clinical local response (tumor control) is significantly better in the complex treatment than its counterpart options. However the malignant disease is not local, so we were intensively looking for the systemic (integrative) evaluation, which are the survivals and the quality of life. Both of these parameters are definitely enhanced by the synergy of oncothermia with CIB. It is important to also, how the groups B and C are equivalent ($p>0.9!$), which convinces the researchers that both of the methods are natural and acting in the dynamism of the homeostatic control. Oncothermia disclaims the old approach, introducing a new paradigm: with application of micro-heating it makes considerable less physiological feedback to work against the action, and with application of the electric field it uses such an effect, for what the body has no physiological answer. With this new paradigm oncothermia helps the natural feedback mechanisms to reestablish the healthy state. The philosophy of oncothermia follows simply the line of Hypocrates: “Nil Nocere” (“Do not harm”) Of course this has to be understood on the way as “be natural as more as possible”. This is the basic of the great harmony with the TCM methods, which philosophy based on the same principles. Both the treatment modalities support the natural processes of living organisms, applying the normal physiological, biophysical and biochemical reactions of the body, using these to fight against the malignancy on standard way. This is the solid basis of its application in combination of the TCM methods, and especially with CIB therapy, which concentrates on the immune effects, to keep the effectors of the homeostatic balance forceful.

Both the treatments are very safe, no similar side effects appear as we had seen in most of the MWM methods, like the chemo- and radio-therapies.

Conclusion

Integrative treatment of colon carcinoma with Oncothermia and Clifford TCM Immune Booster is safe and therapeutically effective.

- It can prolong survival time and improve the quality of life of patients.
- Only a few minor adverse reactions appeared which were rapidly resolved in a short time without treatment and had no effect on the quality of life of patients.
- This integrative treatment of Oncothermia and Clifford TCM Immune Booster is an important contribution to the non-toxic approach to treatment of cancer.

The research is in progress for other cancer lesions too.

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