The action of hyperthermia in metastatic colorectal cancer in combination with chemotherapy

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ABSTRACT

Introduction: Hyperthermia is characterized as the fourth pillar in treating cancer, including surgery, chemotherapy and radiation. Clinical studies suggest that the combination of hyperthermia with radiation and chemotherapy, can bring very good results in treating various types of cancer, including colon cancer.

Purpose: To investigate the effects of hyperthermia in metastatic colorectal cancer in combination with chemotherapy.

Materials and methods: A clinical study, which recruited 32 patients with diagnosed colorectal cancer. The patients were divided into a reference group (15 patients), which received chemotherapy and sessions of hyperthermia and in a control group (17 patients), which only received chemotherapy. For the application of hyperthermia, the Celsius 42+ machine was used. Imaging tests were performed before and after taking the regimens, in order to evaluate the effectiveness of each treatment approach.

Results: Through the imaging assessment, a positive outcome of the disease was observed, for the team of hyperthermia (reference group). Specifically, when compared with the control group, the reference group showed a shrinkage of metastatic foci, derived from colon cancer. In contrast, in the control group there was an increase of dimensions compared with hepatic metastases and metastases in the abdomen, while a steady state was maintained regarding thoracic metastases.

Conclusions: The beneficial effects of hyperthermia are undeniable, as year after year resulting more and more clinical trial data that support this view. The consolidation of the application of hyperthermia cancer treatment, is now a matter of time.

Key words: colon cancer, colorectal cancer, treatment, hyperthermia, oncothermia, chemotherapy, supplementary therapy

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INTRODUCTION

Colon cancer is the third most frequently occurring cancer in men and women. Mortality from colorectal cancer is constantly decreasing over the past twenty years. This may be due to the fact that new cases are fewer, are earlier diagnosed and the treatments have greatly improved. The survival rates of patients with colon cancer are largely associated with the stage of the disease. A 70% of cases with localized cancer exceed five-year survival, while in cases with metastases the survival falls below 10%. Regarding the neoplastic colonic disease 40% of cases are diagnosed as adenoma, which is not accompanied by metastasis, another 40% of cases are diagnosed as carcinoma with attendant "invasion" in peripheral lymph nodes, while the remaining 20% of cases the cancer is already metastatic and localized to other organs [1].

Today, the treatment of colorectal cancer, is based on combination therapies, which in most cases include surgery, local radiation therapy and chemotherapy. Of course, the type of treatment, depends on the disease stage [2].

In hitherto data on the treatment of cancer, is added a new and promising method. After 5000 years of practice, doctors of various specialties have used heat therapy to treat cancer [3]. The idea that heat can cure cancer comes from antiquity. Written reports about the use of elevated temperature in the treatment of cancer, exist for many centuries. Probably, the oldest report was identified in the Egyptian surgical papyrus Edwin Smith, who dated around 2500-3000 BC [4]. Hippocrates claimed that cancers are sensitive to high temperatures, and similar was the attitude of Parmenides, who in 540-480 BC said, "give me the opportunity to develop a fever to heal any disease"[5]. Global interest in hyperthermia increased after the 1st International Conference on hyperthermic oncology at Washington in 1975 [4].

Hyperthermia, is a type of therapy, in which the body tissues are exposed to elevated temperature [5]. Apart from hyperthermia, another more specific term its application in cancer, is oncothermia or onco-hyperthermia. The oncothermia, is the selective increase in the temperature of the tumor and his area. The oncothermia tries through warming, to cause inhibition of tumor growth and promote apoptosis of cancer cells [6].

For the study of hyperthermia as a method of treating cancer, experimental animal models were used to treat various types of advanced cancer. After numerous clinical trials hyperthermia has reached clinical applications [7] for treating various types of cancer such as cancer of the liver, breast, pancreas, colon, lung, cervix, uterus (endometrium), ovary, prostate, larynx, testis, stomach, bone, thyroid, esophagus, even malignant melanoma, lymphoma, and tumors in the bladder and brain tumors with significant outcomes [8].

With hyperthermia a selective temperature increase from 41^{o} to 45^{o} C is applied to the tumor area [9,10]. Non-ionizing radiation and specifically microwaves, radio waves, ultrasound and electromagnetic waves are used to apply heat [11]. Hyperthermia can be either local or whole-body [12]. The first is used to increase the temperature of the tumor, while the second for warming the whole body, if exists metastatic cancer. Noteworthy is that in both cases the efficiency of the process relates to the temperature reached during the treatment, the duration of exposure and the characteristics of the cells and tissue which will be exposed [13]. Hyperthermia is a promising method and minimally invasive, because does not affect normal cells [14].

The purpose of this study was to investigate the way, in which hyperthermia reacts on diagnosed metastatic colorectal cancer in combination with chemotherapy. At the same time, it was evaluated whether the complementary treatment of hyperthermia, in combination with standard chemotherapeutic drugs, can bring therapeutic effects in cases of colon cancer.

MATERIAL AND METHODS

Type of research study

A quantitative approach was used. The type of the study is a clinical, comparative and correlation prospective study, in order to answer the following question: What is the effect of hyperthermia in metastatic colorectal cancer in combination with chemotherapy?

Through the quantitative approach and the systematic investigation of correlations and comparisons, secured data were obtained which impart credibility to the findings.

Sample and research environment

The sample of the study comes from private hyperthermia centers in Athens and Thessaloniki, Greece. Specifically, patients were recruited from Balkan Hospital of Thessaloniki and Hyperthermia Centre "Revital" in Athens.

Patient selection criteria:

- Patients aged over 45 years, diagnosed with metastatic colorectal cancer
- Patients receive chemotherapy, according to the oncologist's instructions
- Patients should have done the minimum number of hyperthermia sessions, according to the data of international literature

Exclusion criteria

- Patients who underwent less than 20 sessions of hyperthermia
- Patients who refused to grant chemotherapeutic drugs

Research tool

The hyperthermia machine Celsius 42+ (or Celsius TCS) was used in all hyperthermia sessions. The artificial RF electric hyperthermia applied externally with physical measures, causes, among other things, an increase in tumor temperature and is therefore a perfect complement to chemotherapy and radiation therapy. In this treatment method the patient emulates the insulator between the two active application electrodes. He serves as the capacitor (capacity) between the electrodes and is thus part of a resonant oscillating circuit. Through the capacitive, thermodynamic effects in tissue, currents (heat) are generated. By this arrangement and the free choice of energy input the treatment can be adjusted to the patient, the tumor identity and tumor location [15].

The hyperthermia system has 2 treatment electrodes, which with a maximum power up to 500 watts ensure a high and homogeneous overheating in the tumor tissue. Due to the different electrode sizes the energy input directed against the tumor can be controlled [15].

Study Design

The sample of patients who participated in the study was collected based on the selection and exclusion criteria, mentioned above. It was done non-random sampling, because there are only two centers in Greece, applying the method of hyperthermia. Therefore, it is a convenience sample.

About the limitations of the study, major difficulty was the fact that the method of hyperthermia applied only in the last five years in Greece and in a limited number of hospitals. We recruited 32 patients, divided into two groups, the reference and the control group respectively. Specifically, the reference group (group of hyperthermia), included 15 patients, while the control group consisted of 17 patients. All individuals, regardless of group, came with diagnosed metastatic colorectal cancer. The cases of patients were colon adenocarcinoma, moderately and poorly differentiated. Surgical resection was preceded, while metastases were identified, which included liver, abdominal and thoracic metastases. Specifically, liver metastases were intrahepatic foci in the lobes of the liver. Abdominal metastases were associated with omentum implants, presence of mass in the middle of the transverse colon, ascending colon, blind, mass in front of the sacrum bone and lymph node metastases, which included inguinal, mesenteric, retroperitoneal, paraaortal lymph nodes, well as lymph nodes around the tripod of Haller and the section of Winslow. Thoracic metastases, consisted of foci in the lobes of the lung parenchyma, lymph node metastases, which include axillary lymph nodes and mediastinal lymph node, as prevascular, pretracheal lymph nodes, as well pulmoaortic window lymph nodes.

Regarding the treatment applied to each group, the patients of the control group received chemotherapy, under the oncologist's instructions. The chemotherapy regimens that administered, consisted of drugs such as FOLFOX, FOLFIRI, AVASTIN, Xeloda, Oxaliplatin, 5-FU, Mitomicyn C. The details of treatment, compared with the dosages of the drugs and the way of administration, was tailored to each individual patient and determined by the treating oncologist of each patient.

The reference group received chemotherapy as the control group, but at the same time was subjected to hyperthermia sessions, using the machine Celsius 42+. The duration of each session was one hour. The number of hyperthermia sessions ranged from 20 to 25 and they were applied every 72 hours, two times per week. The values of the power used during any session of hyperthermia, were based on a specific protocol, the applied frequency was 13.56 MHz, while the developing temperature was around 43-44^{o}C (we know the temperature value from the company). Furthermore, two electrodes with a diameter of 250mm each were used.

Data collection

Recruiting of patients and the monitoring of their disease course, was performed in the period of June 2011 to November 2014. Patients of the control and reference groups were classified further into subgroups according to the type of metastases. Essentially, subgroups of secondary metastatic focus were created, depending on their localization. Consequently, three categories of metastatic foci emerged, which respectively were common to both groups (control and reference). These categories were related to liver metastases, metastases in the abdomen and chest. Each category of metastatic foci was analysed separately in the control and in the reference group respectively. Namely, the effect of therapeutic regimens in both groups of patients, in each separate category of metastatic foci were applied.

By using imaging tests, namely CT (computed tomography) and MRI (magnetic resonance imaging), the diameters of the secondary focus, before and after the completion of the therapeutic regimen cycle, were measured for each group. Then these diameters were compared (in the beginning and in the end of the treatment cycle). Additionally, in the group of hyperthermia, the radiological assessment was made one month after the completion of the last hyperthermia session.

Ethics issues

The study was conducted with the permission of the Scientific Council of Ethics and

Ethics Committee of the Department of Nursing of the University of Athens, after the respective submission of a research protocol.

Statistical analysis

The data regarding the size of foci, that emerged through imaging studies (CT, MRI, ultrasound) were described and statistically analyzed with the IBM SPSS Statistics system 22. It should be noted that the descriptive characteristics of nominal variables (categorical), such as sex, are presented as absolute (N) and relative (f) frequency range in percentage (%). The descriptive characteristics of quantitative variables (constant), as the age and the dimensions of metastatic foci, during two measurements, before and after treatment, are presented as average.

RESULTS

About the demographic data of patients in control and hyperthermia groups, observed that the population of the two groups are similar, with two people difference (hyperthermia group 15 and control group: 17). In all patients of both groups, men account a larger percentage (53.10%) compared to women (46.9%). In the hyperthermia group, men account a rate of 66.7% compared with women 33.3%, in contrast with the control group, where men exhibit a smaller proportion (41.1%), compared to women who account for 58.9%. The mean age of patients of both groups show a low degree of deviation of about 3.79 units, which indicates that there are not large ages variations (Table 1).

Table 1. Demographics of reference group (hyperthermia) and the control group

Demographics	Hyperthermia Group N(%)	Control Group N(%)
Patients number	15	17
Sex		
Male	10 (66,7)	7 (41,1)
Female	5 (33,3)	10 (58,9)
Age	65.26[α]	61.47[α]

[α] Mean value

Patients were separated according to receiving treatment regimen (hyperthermia or not) and the localization of metastatic foci, to facilitate correlations and statistical analysis. To control a normal distribution of the continuous variables, Shapiro-Wilk tests were performed, because the sample of patients was less than 50. By using the correlation coefficient of Pearson and the correlation coefficient of Spearman ,we investigated the existence of a relationship between continuous variables, namely measurement of diameter 1 and measurement of diameter 2, in patients groups hyperthermia-liver, hyperthermia-abdomen, hyperthermia-thorax, control-liver, control-abdomen, control-thorax, as shown in Table 2.

Table 2: Correlation between the diameters of foci in the first and second assessment, in patients groups, hyperthermia-liver, hyperthermia-abdomen, hyperthermia-thorax, control-liver, control-abdomen, control-thorax.

	Measurement diameter 1 Mean value 1	Measurement diameter 2 Mean value 2	Statistical control (p)
Hyperthermia-liver	3.175	2.6	<0.001**
Hyperthermia-abdomen	2.7933	2.1967	<0.001**
Hyperthermia-thorax	0.8611	0.5278	0.059*
Control-liver	2.8286	3.8433	<0.001**
Control-ventricle	0.8929	1.0571	<0.001**
Control-thorax	1.2588	1.2588	0.098*

* significance level 0.05; ** significance level 0.01

Furthermore. a comparison of diameters obtained from the two measurements phases, between hyperthermia and control groups, with liver metastases, with abdominal metastases and thoracic metastases respectively. Specifically, in the group of liver metastasis was performed parametric test (Student's *t*-test) with a dispersion analysis (analysis of variance). The results are shown in Table 3 and in Figure 1.

Table 3: Correlations between the foci diameters (cm) on the liver metastases in hyperthermia group and the control group patients

	Mean value (Standard deviation) Hyperthermia group	Mean value (Standard deviation) Control group	Statistical control (p)
Diameter 1	3.1750 (1.94805)	2.8286 (2.12918)	0.629[α]
Diameter 2	2.6 (1.38231)	3.8433 (3.03100)	0.111[α]

* significance level 0.05; [α] dispersion control

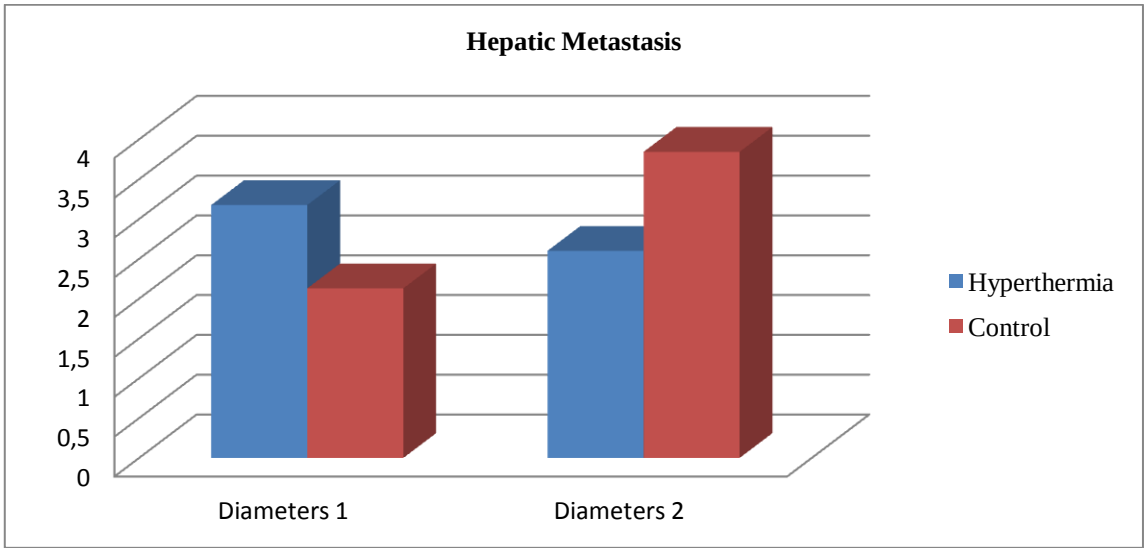

Figure 1: Comparative imaging of foci diameters (cm) on the liver metastases in hyperthermia group and the control group patients, at the beginning and the end of the treatment cycle

Also, in the group with foci in the abdomen, a parametric test (Student's t-test) with a dispersion analysis (analysis of variance) was performed, regarding the foci diameters in the first measurement and non-parametric test, by comparing medians (Mann-Whitney test), during the second measurement (Table 4 and Figure 2).

Finally, in the thoracic metastases group, as shown in Table 5 and Figure 3, a non-parametric test was performed (non parametric test) comparing medians (Mann-Whitney test).

Table 4: Correlations between the foci diameters (cm) on the abdominal metastases in hyperthermia group and the control group patients

	Mean value (Standard deviation) Hyperthermia group	**Mean value (Standard deviation) Control group**	**Statistical control (p)**
Diameter 1	2,7933 (2.47429)	0.8929 (0.45652)	0.011^{α}
Diameter 2	2.1967 (2.21008)	1.0571 (0.64892)	0.021^{β}

* significance level 0.05; $^{\alpha}$ dispersion control; $^{\beta}$ compared interstitial

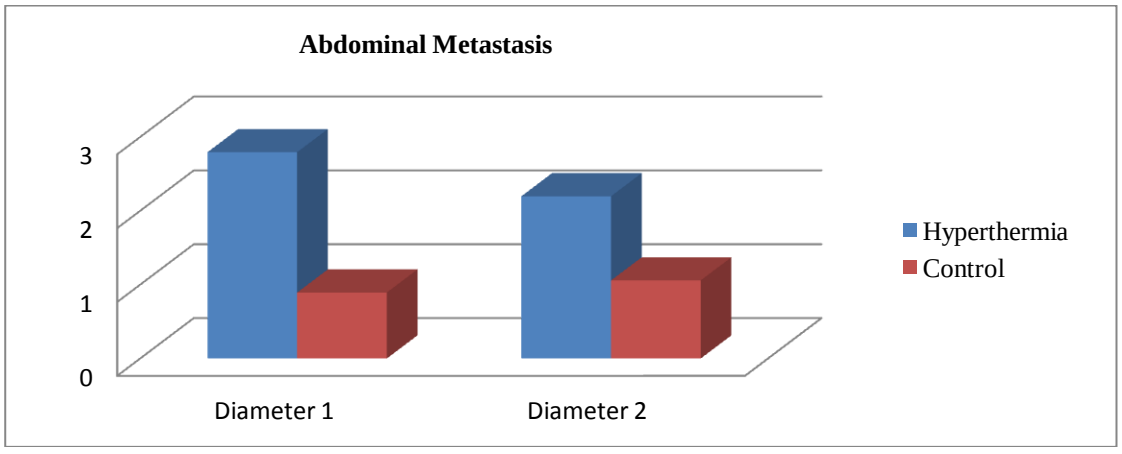

Figure 2: Comparative imaging of foci diameters (cm) on the abdominal metastases in hyperthermia group and the control group patients, at the beginning and end of the treatment cycle

Table 5: Correlations between the foci diameters (cm) related to thoracic metastases in hyperthermia group and the control group patients

	Mean value (Standard deviation) Hyperthermia group	Mean value (Standard deviation) Control group	Statistical control (p)
Diameter 1	0,8611 (0.45811)	1.2588 (1.19951)	0.534$^{\beta}$
Diameter 2	0.5278 (0.46577)	1.2588 (1.91379)	0.255$^{\beta}$

* significance level 0.05; $^{\beta}$ compared interstitial

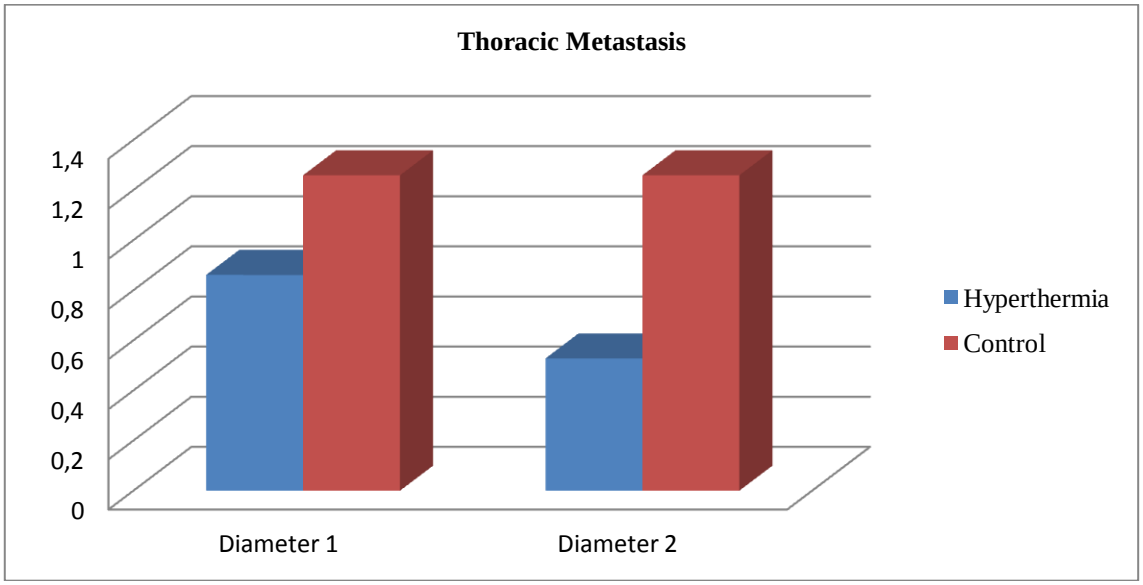

Figure 3: Comparative imaging of foci diameters (cm) related to thoracic metastases in hyperthermia group and the control group patients, at the beginning and end of the treatment cycle.

RESULTS

Patients of both groups were studied according to the type of metastases. Three categories of research were created, which concerned liver metastases, metastases in the abdomen and chest metastases. The behavior of metastatic foci was studied, regarding the change of dimensions, namely their diameters, after taking the prescribed treatment regimen, in the reference and control group respectively.

Specifically, the category of hepatic metastases, as shown in Table 3 and Figure 1, in the reference group (hyperthermia group), showed a decrease of the mean value of the foci diameters (from 3.175cm to 2.6 cm), after receiving hyperthermia in combination with chemotherapy. This decrease corresponds to a rate of 18.1%. In contrast the control group, which received only chemotherapy regimen, increased the mean value of the diameter of metastatic liver foci (from 2.8286 cm to 3.8433 cm), which represents a rate of around 35.87%.

Moreover, in the category of metastases in the abdomen, according to Table 4 and Figure 2, the group of hyperthermia showed a decrease of the mean value of the metastatic foci diameters (from 2,7933 cm in 2,1967cm), after the combination treatment with hyperthermia and chemotherapy. This reduction represents a rate of 21.36%. In contrast, the control group showed an increase of the mean value of the foci diameters (from 0.8929 cm to 1.0571 cm), by 18.9%.

Also, in the third category, which concerned thoracic metastases, according to Table 5 and Figure 3, in the reference group there was a reduction in the mean value of the thoracic foci diameters (from 0.8611 cm to 0.5278 cm), which corresponds to 38.71%. In the control group no change was observed in the mean value of foci diameters (from 1.2588 cm to 1.2588 cm). Therefore the percentage change corresponds to 0%.

DISCUSSION

Colon cancer is the second leading cause of deaths related to cancer in Europe and the USA. Death from colon cancer represents approximately half a million a year, worldwide. Statistics do not show specific differences between the sexes, but is prevalent in ages over fifty. Genetic and

environmental factors have a clear role in the development of colon cancer. It is estimated that 80% of cases came from environmental sources, associated with alcoholic beverages, low consumption of vegetables and folic acid, increased fat, diet with red meat and smoking. Surgical resection remains the main treatment for colon cancer. The primary postoperative prognosis is the stage of the disease. Patients who have not distant metastases, survive more than five years, at around 75%, while the metastatic cases show very less survival rate. Of course, many kinds of supplementary treatments, are used to prevent possible recurrence and growth of metastatic damages [16].

Regarding chemotherapy, one of the older standard protocols for colorectal cancer is the adjuvant fluorouracil (5-FU) in combination with leucovorin [17,18]. Irinotecan was developed for cases, in which the protocol with fluorouracil + leucovorin was not effective [19,20]. For comparison of three different action mechanisms of the chemotherapy, were applied in advanced colorectal cancer therapies with fluorouracil, irinotecan and oxaliplatin [21,22]. The mechanism of irinotecan and oxaliplatin, is different compared to the mechanism of fluorouracil and so the synergy is expectable [23,24]. So by the middle of the last decade, therapy of colon cancer was standardized by three active agents: 5-fluorouracil (+ leucovorin), oxaliplatin and irinotecan [25-27]. A large clinical study with 2135 patients with advanced colorectal cancer who had poor prognosis was performed [28]. The Kaplan-Meier survival test, showed a significant advantage of combined therapies. The disadvantages of chemotherapy, are including side effects of these drugs and the fact that patients often develop multidrug resistance (MDR), which inhibits further chemo-applications. Immunotherapy is one of the non-chemical methods for the treatment of colon cancer. Instead of chemotherapy, there are other approaches, including the use of antibodies and vaccines, which could be particularly effective in treating metastatic disease [29-31]. Another strategy is the anti-angiogenic therapy, which is less toxic than conventional chemotherapies and has a lower risk about drug resistance [32].

Furthermore, in the treatment of colorectal cancer, except chemotherapy is also included radiotherapy. The type of treatment, as well as the survival rates, depend on the stage of disease again. Therefore, an important role plays the staging of the cancer, which is based on the primary volume (step T), the involvement of lymph nodes (N phase) and the appearance of distant metastases (M stage) [33].

Additionally, as the fourth pillar in the treatment of cancer, is considered now hyperthermia, next to chemotherapy, radiotherapy and surgery. Hyperthermia is approved as a medical method by the Greek National Organization for Medicines (EOF). Also it is applied by the biggest international oncology centers, in order to assist and enhance patients, suffering from almost every type of cancer.

Through this clinical study and the results that emerged from this research, it appears clearly that the combination of hyperthermia and chemotherapy can provide a better result on the course and treatment of disease, in metastatic colorectal cancer cases.

The survey data show that the combination treatment of chemotherapy and hyperthermia, can lead to shrinkage of metastatic foci that are detected in the liver and abdominal and come from a primary focus in the colon. In contrast, patients who received chemotherapy alone, showed worsening of the disease accompanied by increasing of liver metastases size and metastatic foci in the abdomen.

Also, on the thoracic metastases from colorectal cancer, the combination of hyperthermia and chemotherapy, was proved as effective as in the previous categories. In particular, a decrease in the size of metastatic foci, which were located in the thoracic cavity, was noticed. Regarding the group of patients who received only chemotherapy, was found a stationary state. Namely, thoracic metastases showed no change in their dimensions.

Furthermore, through the international literature, is reinforced the view on the synergistic action of hyperthermia with chemotherapy in patients with advanced colorectal cancer. Through the studies, accrue very good results regarding the above therapeutic combination [34]. More specifically, in recent studies about chemotherapy, the treatment response rate in colon cancer, which included administration of 5FU/LV (fluorouracil/ leucovorin) by addition of irinotecan was 22% and led in survival of 6.3 months. Compared with hyperthermia, the objective response rate was 33%, while the average overall survival was 12 months (2-28 months). This study of hyperthermia concluded that hyperthermia does not increase the toxicity of the treatment with 5FU/LV/irinotecan, while demonstrated the benefits of combined treatment. Additionally, it has been reported the application of hyperthermia preoperative [35,36]. A phase II study with locally advanced rectal cancer supported the feasibility of preoperative application of hyperthermia [37]. Furthermore, embodiments of preoperative hyperthermia are characterized of success in combined approach (chemotherapy, radiotherapy and hyperthermia) [38].

Also, a study conducted, which included 218 patients (n=218). Patients were classified for rectal cancer (n=92), colon (n=114) and sigmoid (n = 12). The oncothermia was applied 2-3 times a week, for 6-12 treatments, using electrode diameter 20 cm. The survival rate for the first year of the oncothermias implementation was 84.9% [39].

Studies were performed for the most common remote metastases of primary colorectal cancer and especially for secondary malignancy in the liver. A study was conducted on the preoperative application of oncothermia in liver metastases originating from colorectal cancer. There was used combined therapy and specifically: radiation: 45 + 5 Gy (fractional), chemotherapy: 5-FU/Mitomicine-C (2x), oncothermia: 60 min, diameter 30 cm (8-10x). The results showed that after oncothermia, 71% of patients took complete resection (R0), while a patient was partially excised (R1) and one patient is not operated successfully (remained R2) [40].

It is worth mentioning, that one of the first studies of oncothermias for colon cancer with liver metastases (n = 80), was published in 1999 [41]. The median survival was significantly greater in patients receiving oncothermia. The median overall survival was expected at 11 months, but for patients who underwent in oncothermia, the median survival time was 24.4 months, while patients who received chemotherapy and complementary oncothermia, median survival was 21.5 months. Moreover, another study on liver metastases derived from colorectal cancer, was presented at the ASCO conference. The local clinical response of liver metastases corresponded to a rate of 28%. At the same time, better quality of life was reported in 50% of patients [42].

Moreover, another study was devoted to compare the first line therapy (without oncothermia) and second line (with oncothermia) for colorectal cancer with liver metastases (n=15) [43]. The local response following the second line treatment was significantly better compared to the first line treatment, without additional toxicity for patients. Also, tumor progression was observed mainly outside of the applied electromagnetic field. Additionally, a first-line phase II study (n=30), compared the effect of platinum derivatives, in liver metastases from colorectal cancer [44]. It was found that the platinum derivatives, show a response rate of 20%, and improve quality of life by 50%. There was also a reduction of anxiety (83% of patients), while nausea and vomiting occurred in 13.3%, while the other effects were located in less than 10% of patients. Of course, a side effect of oncothermia, which included erythematous and mild fatty burn, was observed in 6.7% of patients [44].

Additionally, an independent study was conducted. In this study was compared treatment with oxaliplatin and oncothermia (n=12) and treatment with cisplatin and oncothermia (n=18) and arose specific differences. The percentage of the local response was definitely higher in cisplatin therapy. This study was made for advanced rectal cancers (n = 65) and hepatic metastases (n=29) 299. The oncothermia was applied 2-3 times a week, with concomitant administration of chemotherapy. Overall, the clinical response was 96% for the colorectal and 86% for liver metastaseis [16].

A study was conducted, in which were used two groups of patients with colorectal cancer. One group received chemotherapy, while the other group of patients received hyperthermia and chemotherapy. In the hyperthermia group, therapy was applied with RF, twice a week for 60 minutes. The effects were evaluated before and after the treatment. The effectiveness rate, by the combination of chemotherapy with hyperthermia corresponded to 44.11%, while for the group of patients who received chemotherapy alone, the rate was 35.29%. Therefore was found a good therapeutic effect, but also a clinical benefit from the combination by chemotherapy with hyperthermia using radio frequencies, for patients with advanced colorectal cancer. From the combination no side effect was mentioned [45].

At the same time in another research, was studied the efficacy of local hyperthermia (HT) when applied together with chemotherapy and radiotherapy. A total of 808 patients was treated with radiation (RT) and chemotherapy (CT), in combination with the local HT (hyperthermia). Of the 808 patients, 688 received radiotherapy with local hyperthermia, which was consisted of 443 cases of deep-hyperthermia, 165 cases hyperthermia surface and 80 cases were treated with chemotherapy, radiotherapy and deep-hyperthermia. Also 120 patients out of 808, received chemotherapy in combination with local hyperthermia [46]. The medical instruments that were used for hyperthermia, were made by Xuzhou Nuowan and include deep HT machine (433MHz) and surface HT machine (915MIz). The patients were submitted in 4 to 12 hyperthermia sessions. Also each session lasted 40-60 minutes and the temperature varied between 38.5 ℃ and 41.5 ℃. In addition to radiotherapy, was used 6~8 MV-ray or electron beam, while chemotherapy designed based on the types of tumors and patients were treated by one to four cycles of chemotherapeutic drugs. Patients who received combined RT + CT + HT, took two cycles of the regimen. The results showed that the efficiency rate for radiotherapy with deep hyperthermia was 71-91%, radiotherapy and hyperthermia surface was 86-96% and radiotherapy-chemotherapy and deep hyperthermia was 75-100%. In contrast, the efficacy rate of chemotherapy with deep hyperthermia was 57.5%.

Therefore, the study showed that the efficiency rate of the combinations of RT + HT or RT + CT + HT was more than 80%. The combination therapy with RT + HT exhibits significantly better efficiency rate compared with RT alone. However, as mentioned above, the efficiency rate of the combination CT + HT is only 57.5%, that may be due to low concentration of

drugs in the tumor or cell resistance in the drugs [46].

Also in one study were used 123 patients with colorectal cancer. The patients were randomized into 3 groups, namely, 57 cases in the group that received chemotherapy with FOLFOX (group A), 35 cases treated with chemotherapy plus invasive treatment (group B) and 31 cases treated with chemotherapy plus hyperthermia treatment that lasted one hour (group C). These treatments were repeated every 3 weeks for 8 cycles total. The results showed that among 123 patients, disease-free survival duration of three years for groups A, B and C were 71.9%, 77.1% and 77.4% respectively ($p = 0.793$, not statistically significant). The five-year survival rates of groups A, B and C were 56.1%, 57.1% and 58.1% respectively ($P = 0.984$, not statistically significant). So in all categories found greater survival rate for the group of hyperthermia, compared with other groups. Therefore, the combination of hyperthermia with FOLFOX as postoperative adjuvant treatment for colon cancer is safe and effective [47].

CONCLUSIONS

Hyperthermia is a multifaceted form of medical treatment, wherein the tumor tissue is exposed to elevated temperatures, with the aim of destroying the cancer cells, taking advantage of the synergistic action with chemotherapy and radiation. This treatment is simple and painless.

Hyperthermia in no way reduces, cancels or impedes the other methods. Instead, most scientific studies that have been performed, combine hyperthermia with chemotherapy and / or radiation, fully confirming the synergistic effect of all this, with impressive results for the length and quality of life of the patient.

As demonstrated by this study in advanced colorectal cancer, hyperthermia in combination with chemotherapy, may provide a better therapeutic effect, compared to chemotherapy alone.

The results showed a reduction of metastatic foci in patients who underwent hyperthermia sessions.

The beneficial effects of hyperthermia are undeniable, as year after year resulting more and more clinical trial data that support this view. Therefore, the consolidation of the application of hyperthermia cancer treatment, is now a matter of time.

Conflicts of interest

None declared

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