Initial publication

Updates of the application of regional hyperthermia in the treatment of esophageal, colorectal, and pancreatic cancers

Giammaria Fiorentini[1,2], Donatella Sarti[1], Girolamo Ranieri[3], Cosmo Damiano Gadaleta[4], Caterina Fiorentini[5], Tommaso Carfagno[6], Carlo Milandri[7], Andrea Mambrini [8], Stefano Guadagni[9]

[1]Department of Onco-Hematology, Azienda Ospedaliera "Ospedali Riuniti Marche Nord"
Pesaro, Italy
[2]Oncology Service and Unit of Hyperthermia, Private Clinic Ravenna33,
Ravenna, Italy
[3]Interventional and Integrated Medical Oncology, National Cancer Research Centre,
IRCCS Istituto Tumori "Giovanni Paolo II",
Bari, Italy,
[4]Integrated Section Translational Medical Oncology, Interventional Radiology Unit,
National Cancer Institute of Bari,
Bari, Italy
[5]Department of Medical Biothecnologies, Division of Cardiology, University of Siena,
Siena, Italy
[6]Department of Radiotherapy, University Hospital of Siena,
Siena, Italy
[7]Medical Oncology Unit, San Donato Hospital
Arezzo, Italy
[8]Oncology Department, Apuane Hospital,
Massa-Carrara, Italy
[9]Applied Clinical Sciences and Biotechnology, Section of General Surgery, University of L'Aquila,
L'Aquila, Italy

Citation: Fiorentini G. et al. (2021): Updates of the application of regional hyperthermia in the treatment of esophageal, colorectal, and pancreatic cancers, initial publication: Oncothermia Journal 30: 20 – 36,
http://www.oncotherm.com/sites/oncotherm/files/2021-04/Fiorentini_Updates.pdf

Abstract

The therapeutic value of regional hyperthermia (RHT) in oncological treatments has been known for years. Several studies report RHT efficacy for tumor response and survival. RHT can also be used in combination with chemotherapy (CHT), radiotherapy (RT), chemoradiotherapy (CRT), and immunotherapy, enhancing their benefit, also in the treatment of gastrointestinal tumors as esophageal, colorectal, and pancreatic cancer. However, RHT has not yet become a common therapy in regular clinical practice due to the difficulty in measuring the temperature increase inside the tissues, the long duration of treatment, the need to have dedicated nurses and doctors, adequate equipment and facilities.

Modulated electro-hyperthermia (mEHT) is a recent RHT method that targets malignant cell membranes and the extracellular matrix, allowing deep tumor sensitization, notwithstanding the adipose tissue's thickness and overcoming the issue of homogenous heating.

Several studies confirm the advantage of RHT and mEHT association to CRT, CHT, and RT as neoadjuvant and palliative setting in esophageal, colorectal, and pancreatic cancer. This article summarizes the available data of RHT for these tumors.

Key words: regional hyperthermia, modulated electro-hyperthermia, colorectal cancer, esophageal cancer, pancreatic cancer

Introduction

Regional hyperthermia (RHT) efficacy in remission of malignant tumors has been known for decades. RHT increases the tissue/body temperature with an external radiofrequency (RF) electromagnetic field. The modern technologies of local/locoregional heating offer safe therapies in clinical practice. The mild temperatures of RHT (39.5–43°C) show beneficial effects accompanied with increased safety by optimizing the treatment for minimal hot spot occurrence [1], [2]. Temperature rise >43°C, indeed, has potential risks, such as damage of surrounding normal tissues and enhancement of blood flow that can potentially increase malignant cells dissemination and distant metastases [3].

Nowadays, an increasing number of clinical studies show RHT efficacy in the treatment of different types of cancers. However, the number of clinics using the RHT method in their practice is suboptimal [1].

The primary biological rationale of heat utilization is enhancing radiation efficacy, increasing the delivery and permeability of various chemotherapeutic medications, and supporting the immunotherapy effects. Heat triggers tumor perfusion and oxygenation changes, inhibiting DNA repair mechanisms and stimulating the immune system [1], [2]. In association with RHT, local radiotherapy increases tumor immunogenicity and systemically acts through immune-mediated abscopal effects [3]. Modulated electro-hyperthermia (mEHT) is a recent RHT method that targets malignant cell membranes and the extracellular matrix, allowing deep tumor sensitization, notwithstanding the adipose tissue's thickness. The complementary application of regional hyperthermia and mEHT with chemo-(CHT) or radiotherapy (RT) is reported to be successful in several types of tumors, including esophageal, pancreatic, and colorectal cancers [3], [4], [5].

The analysis of elder evidence-based clinical data of the five-year survivals concluded [6], that the 5-year survivals have been changing only a little from 1950 to 1995, and these changes depend more on the better diagnosis than on the therapy. The contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults (counting 22 different localizations) was estimated to be 2.3% in Australia and 2.1% in the USA [7] in 2004 over 20 years. It is a minor contribution to the observed 5 years survival rate, which is over 50% in the same time period.

The progress, of course, was debated: "We are losing the war against cancer" [8], which was immediately corrected in a broader view, [9], taking into account the successes in pediatric cancer and in the quality of life of the patients during the curative and palliative treatments. This picture was a little diluted: "Perhaps not lost, but

certainly not won." [10]. This was also supported ten years later [11]. The emotional aggravation induces very hurting opinions as the double Nobel-laureate L. Pauling formulated it, "Everyone should know that the 'war on cancer' is largely a fraud" [12]. This is naturally hurting but copmpletely false opinion, which was induced by this excellent researcher's heated emotional background. The emotions are not surprising even nowadays because cancer is the number one disease in many countries, touching not only the suffering patients but also their families, friends colleagues, and motivating despair in society.

Filtering out the extreme opinions, the statistical data [13] supported the shadowed picture even 20 years ago: the mortality data from 1975-2000 are fairly constant, while the incidence (morbidity) slightly grows in the same time-internal. (Interestingly, the incidence has a definite peak in the first half of the 1990s in the group of males, but the mortality does not follow it.) Unfortunately, neither the incidence-rate nor the mortality rate correlated with the five-year survival [6] for the same localization. It showed the imperfectness that cancers with high incidence- and high mortality-rate growths, like lung, liver, brain, and pancreas, had low gain in their 5-year survival in that time. This is the essence of the negative answer to the question [6]: "Are increasing 5-year survival rates evidence of success against cancer?" Today the situation had improved dramatically. We have a significant improvement in mortality data, significantly elongated survival time characterizes the nowadays development, however, in the area of gastrointestinal cancer, especially in pancreatic localization, we see less development of successes of conventional therapies than for other localizations in the human body.

Our objective is to show the possible addition to the conventional therapies by complementary application of hyperthermia. We review the updated clinical applications of RHT complementary with RT and/or CHT in the therapies of esophageal, colorectal, and pancreatic cancers. We include into this review a new emerging hyperthermia method: the modulated electro-hyperthermia (mEHT), which has promising data in gastrointestinal treatments [14], [15] in neoadjuvant treatment [16], [17], or complementary to adequate CHT, treatment of the frequent colorectal metastases in liver [18]. The feasibility of mEHT in the therapies of pancreatic cancer is especially promising [19], [20], [21].

Types of hyperthermia

There are different hyperthermia types: superficial hyperthermia, deep/regional hyperthermia, whole-body hyperthermia, interstitial hyperthermia, intraperitoneal laparoscopic hyperthermia, of hyperthermia in the body cavities or lumens. [22].

Whole-body hyperthermia increases the entire body's temperature up to a maximum of 41.8°C, using thermal conduction or radiant infrared techniques. Interstitial hyperthermia places heating electromagnetic devices (needles or catheters) directly inside the tumor. This therapy's main advantage is that the heating occurs directly inside the tumor, enabling it to reach higher local tumor temperatures and lower normal surrounding tissue temperatures. Similarly, hyperthermia can be achieved by inserting heating devices into natural body cavities and lumens with tumors [22]. Deep/regional hyperthermia can increase the temperature of a portion of the body (at the tumor site) up to the depth of >5 cm with electromagnetic fields, minimizing the heating of the surrounding tissue [22].

Superficial hyperthermia heats tissues <5cm in depth from the body's surface, using electromagnetic fields. As in all types of hyperthermia, the blood flow variability within the treated region also contributes to the temperature variation within the tumor region [22].

Regional Hyperthermia

Different methods are used for regional hyperthermia, such as using infrared-A (IR-A) radiation, microwave radiation by antenna-array, capacitive, and modulated electro-hyperthermia techniques.

The water filter IR-A radiation method uses a light source (halogen lamp at 24 V/150W) and a water-filter which is built in as a closed cuvette and absorbs the energy, avoiding painful sensations and burns of the skins [23]. Both IR-A radiation microwave radiation and capacitive systems are used for superficial hyperthermia to tumors

infiltrating up to 4 cm into the tissue, such as melanoma [24]. Two electrodes are positioned on opposite sides of the body, and the heat is produced by the electric current flowing between them. The electrodes are placed in direct contact with the body surface through a water bolus.

There are several types of commercially available radiative superficial systems, including flexible microwave applicators. They all create heating at frequencies of 434 to 915 MHz and are positioned directly in contact with the treated surface [24]. Both methods allow to homogeneous target heating and limiting hot spots. However, radiative heating yields more favorable temperature distributions than capacitive heating, especially within heterogeneous tissues [24].

Modulated electro-hyperthermia

Tumor blood flow increase is rather limited upon heating; hence, the heat dissipation is slower than that in normal tissues. This is why tumor temperature rises higher than that in normal tissue during hyperthermia [3]. However, a tumor's homogenous heating to a specified temperature is rather challenging due to the heterogeneous distribution of vasculature inside malignant tissue. The tumor blood flow varies widely among different tumor types and inside the same tumor, especially in the presence of necrotic areas within the tumor [3].

A new method has been recently developed to improve the results and reduce thermal therapy's adverse effects: the modulated electro-hyperthermia (mEHT) [25]. This method targets malignant cell membranes and the extracellular matrix. This allows sensitizing deep tumors, notwithstanding the adipose tissue's thickness, and to heating the malignant cells [9] selectively. mEHT uses impedance coupled capacitive arrangement with 13.56 MHz (EHY-2000+, OncoTherm Ltd., Germany) and has comparable benefits to other types of hyperthermia for a variety of tumors: hepatocellular carcinoma, rectal, cervical, brain, lung, and pancreatic cancers, improving local disease control and in some cases, the survival [25], [26], [27], [28], [29]. This type of hyperthermia increases malignant cells' temperature to 41.5°C for >90% of treatment duration [26].

Literature search

The literature search was performed in this narrative review in the databases PubMed-MEDLINE, Embase, Cochrane, and ClinicalTrials.gov. with the search terms: hyperthermia, pancreatic, gastrointestinal, esophageal, colon, rectal, colorectal, anal cancer. 934 articles were retrieved. The further selection included only full-text articles in the English language, reporting results from the observational or experimental trial about tumor response, survival or progression-free survival or toxicity, among these were published in the time interval between 2000 and 2020. We selected 38 articles and divided these according to tumor type, and finally, only 25 original articles were included in tables. The other papers were used for the introduction and conclusions sections.

Esophageal Cancer

The prognosis of esophageal cancer remains poor, and the overall survival (OS) after potentially curative surgery is 5–20% [30], [31]. Several studies on neo-adjuvant chemotherapy (NCHT) alone fail to prove the benefit of this pre-operative treatment. However, promising results have been achieved with the combination of heat and chemotherapy in this setting [31], [32], [33], [34].

NCHT or chemoradiotherapy (CRT) combined with RHT have positive results concerning survival and tumor response of esophageal cancer patients (table 1).

Table 1) Esophageal cancer

Author	Year	Treatment	Hyperthermia protocol	No. of Pts. (n)	Survival	Tumor Response	RHT related toxicity
Sheng [34]	2017	CRT with cisplatin-based regimens+RHT	Radiofrequency capacitive heating device, with microwave spiral strip applicators, HRL-001, within 30 min from RT, or 2h after CHT	50	3-year OS=42.5% PFS= 34.9%	ND	Pain (G1-2) =38.0%
Nishimura [29]	2015	CRT with cisplatin/5-fluorouracil, oral fluoropyrimidine and irinotecan+RHT	8-MHz radiofrequency, capacitive heating system (Thermotron RF-8), at 400-1400 W (median 1200 W) for 50 min once or twice a week	11	1 year OS=72.7% 2 years OS=54.5% 5 years OS=9.1%	CR=27% SD=45%	ND
Nakajima [32]	2015	CRT with docetaxel + RHT	ND	24	3 years OS=56.3% 5 years OS=50.0%	DCR=41.7% CR=17.6%	toxicity G2 occurred in six patients
Hulshof [33]	2009	Neoadjuvant CRT with carboplatin and paclitaxel+ RHT	home-made AMC (academical medical center), phased array of four 70MHz antennas, at a power of 800 W for 1.5 hour	28	1 year OS=79% 2 years OS=57% 3 years OS= 54%	CR=19% PR=31% SD=23%	pain (sternal or shoulder) or general discomfort in seven patients and in two patients
Albregts [31]	2009	Neoadjuvant CHT with cisplatinum and etoposide+HRT	home-made AMC (academical medical center), phased array of four 70MHz antennas, at a power range of 800-1000 W	26	1 year OS=86% 2 years OS=76%	CR=9%	Discomfort in 1 patient and 'sock-like' sensory neuropathy (G2) in 1 patient

RT = radiotherapy, RHT = hyperthermia, OS = overall survival, SR = survival rate, Clinical benefit = complete response + partial response + stable disease, CHT = chemotherapy, DFS = Disease free survival, CRT = chemoradiotherapy, LRFS = local relapse-free survival, n.s. = not significant, ND = not reported

Neoadjuvant CRT with docetaxel associated with RHT results in a response rate of 41.7% with a CR of 17.6% after surgery. This treatment has low toxicity, and 3- and 5-year survival rates are 56.3% and 50.0%, respectively [34].

A phase II study with chemotherapy (carboplatin and paclitaxel) and radiotherapy in association with RHT as neo-adjuvant treatment results are in good locoregional control and overall survival for esophageal cancer patients that have all R0 resection. Tumor response is complete response (CR), partial response (PR), and stable disease (SD) in 19%, 31%, and 23% of patients, respectively. The survival rates at 1, 2, and 3 years are 79%, 57%, and 54%, respectively. Quality of life is improved for these patients, and the toxicity is low [33]. Similar results in survival are reported by another phase I/II study, showing 1- and 2-year survival rates of 69 and 62%, respectively [31].

Intensity-modulated radiotherapy (IMRT) in association with hyperthermia results in a 3-year progression-free survival (PFS) rate and overall survival (OS) rate was 34.9% and 42.5%, respectively, with low toxicity and excellent local control of esophageal cancer with supraclavicular lymph node metastasis [34].

The results of a meta-analysis comparing the CRT+RHT and RT groups show that RHT increased significantly the 1-, 2-, 3- and 5-year OS of esophageal cancer patients; decreased both recurrence, distant metastases, and gastrointestinal reaction rates [30]. This evidence of CRT+RHT benefits in esophageal cancer neoadjuvant therapy is very promising. However, further randomized clinical trials with a more significant number of patients are required to confirm these data.

Colorectal cancer

Colorectal cancer (CRC) is the third most common cause of cancer death in both men and women in the United States [35]. In the past decades, neoadjuvant radiotherapy alone or in association with chemotherapy followed by surgery has become standard treatment for advanced rectal cancer [36]. CHT is used to enhance RT effects of radiotherapy. RHT is another method to amplify radiotherapy, overcoming the low oxygen concentrations that are present in large size tumors and hamper the effect of radiotherapy. RHT, indeed, increases the tumor blood flow and hence promotes the RT with the tissue oxygenation [37].

Neoadjuvant CRT + RHT results in greater 5-year long-term local control (98% vs 87%, p=0.09) and OS (88% versus 76%, p=0.08) than CRT alone in locally advanced non-metastatic rectal cancer [38]. Similar results are reported in other studies on neoadjuvant CRT + RHT in locally advanced non-metastatic rectal cancer, resulting in 5-year OS ranging 60-87.3% (table 2), distant metastases-free survival (DMFS) and local control (LC) of 79.9% and 95.8% respectively [39], [40], [41].

In particular, a study compares OS of CRT alone or combined with RHT and reports that the complementary therapy shows longer OS than CRT alone (5 years OS=76% versus 88% $p < 0.08$) [38]. This improvement in survival is also observed when the neoadjuvant CRT and RHT is performed for anal cancer treatment with 5 years OS (95.8 vs. 74.5%, $P = 0.045$), disease-free survival (DFS=89.1 vs. 70.4%, $P = 0.027$), and the local relapse-free survival (LRFS =97.7 vs. 78.7%, $P = 0.006$) is more favorable than CRT alone [42].

As concerning the tumor response, the disease control rates (DCR) of CRT combined to RHT range is 28.5%-94.8% in rectal cancer patients (table 2) [43], [44], [45], [46], [47]. The association of RHT to CRT in neoadjuvant treatment of rectal cancer does not increase the toxicity of CRT, and the hyperthermia-related adverse events were mainly of mild-moderate intensity and are reported by 26-34% of patients [43], [44], [45], [46], [47].

mEHT in association with CHT is used in a study for the treatment of metastatic colon cancer patients with good tumor response rates and survival; indeed, the DCR is 95% at 90 days and 89.5% at 3 months, and PFS is 12.1 months (range 3.5–32.6 months) [48]. Another study applies mEHT in association with CRT to treat rectal cancer patients, reporting minimal, moderate, near-complete, and complete regression of primary tumor of 15.0%, 51.7%, 18.3%, and 15.0%, respectively [49]. In both studies, the mEHT is well tolerated, with mostly mild hyperthermia toxicity [48], [49].

Table 2) Colorectal and anal cancer

Author	Year	Type of tumor	Treatment	Hyperthermia protocol	No. Pts. (n)	Survival	Tumor Response	RHT related toxicity
Ranieri [49]	2020	Metastatic colon cancer	CHT with Beva+FOLFOX4+mEHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	40	PFS=12.1 months (range 3.5–32.6 months).	90 days: PR=30% SD=65% PD=5% DCR=95% 3 months: CR=5.3%, PR=26.3%, SD=55%, PD=10%, DCR=89.5%	mild positional pain in four patients, Erythema in the target area in 3 patients, power-related pain occurred in two cases
You [48]	2020	Rectal cancer	Neoadjuvant CRT with 5-fluorouracil or oral capecitabine+ mEHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	60	ND	minimal, moderate, near total, and total regression of primary tumor was 15.0%, 51.7%, 18.3% and 15.0% respectively.	26.7% developed thermal toxicity, which was mostly G1 (93.8%)
Zwirner [39]	2018	Locally advanced rectal cancer	Neoadjuvant CRT with 5-fluororuracil +RHT	Deep regional hyperthermia once or twice a week	86	5-years OS =87.3% DFS =79.9 LRFS =95.8%	ND	ND
Gani [38]	2016	Rectal cancer	Neoadjuvant 43 CRT with 5-fluororuracil vs 60 CRT with 5-fluororuracil +RHT	RHT with Sigma Eye or Sigma-60 applicator (BSD 2000/3D) once or twice a week	103	5-years OS= 76% vs 88% p < 0.08 DFS= 73% vs 78% LRFS =77% vs 75%	ND	ND

Author	Year	Type of tumor	Treatment	Hyperthermia protocol	No. Pts. (n)	Survival	Tumor Response	RHT related toxicity
Shoji [43]	2015	Rectal cancer	Neoadjuvant CRT with Capecitabine+RHT 33 were resected 16 non-resected	RHT with 8 MHz RF capacitive heating device (Thermotron RF-8) after RT for 50 minutes (5 weeks)	49	ND	DCR=28.5%	One grade 3 patient had perianal dermatitis, 29.7% suffered pain, and 2.1% had subcutaneous induration
Kato [44]	2014	Rectal cancer	Neoadjuvant CRT+RHT	RHT with Thermotron RF-8, Once a week (2-5 times)	48	ND	CR=29.2%	No hematological toxicity
Schroede [45]	2012	Locally advanced rectal cancer	Neoadjuvant 61 CRT with 5-Fluorouracil+RHT vs 45 CRT with 5-Fluorouracil	RHT with BSD-2000 Once or twice a week (1-9 times)	106	ND	pCR rate 16.4% vs 6.7%	34% hyperthermia discontinuation, due to pain or hot-spot phenomena, urinary tract infections, hypertension, tachycardia or severe skin toxicity
Kang [47]	2011	Locally advanced rectal cancer	Neoadjuvant CRT with 5-FU, leucovorin and mitomycin C+RHT	RHT with 8-MHz radiofrequency capacitive heating device (Cancermia GHT-RF8) twice a week during RT	214	5 years OS=73.9% DFS=75.1% LRFS= 93,9% DMFS= 79.8%	DCR=50.9%	ND

Author	Year	Type of tumor	Treatment	Hyperthermia protocol	No. Pts. (n)	Survival	Tumor Response	RHT related toxicity
Maluta [40]	2010	Locally advanced rectal cancer	Neoadjuvant CRT+RHT	RHT with BSD-2000 Once a week (1-5 times)	76	5-years OS=86,5% DFS=74,5% LRFS= 73,2%	CR=23,6% DCR=94,8%	G0-2 general or local discomfort in 15%, no G3, G4 Subcutaneous burns in 5.2%
Rau [41]	2000	primary rectal cancer (PRC) recurrent rectal cancer (RRC)	Neoadjuvant CRT with 5-fluororuracil and leucovorin +RHT	RHT with BSD-2000 Once a week (1-5 times)	37 18	5-year OS=60%	DCR=59% DCR=28%	none
Ott [42]	2019	Squamous anal cancer	CRT with 5-fluororuracil and mitomycin C vs CRT with 5-fluororuracil and mitomycin C + RHT	RHT with the BSD 2000-3D- and BSD 2000-3D-MR-Hyperthermia System once or twice weekly (5-10 times)	112	5 years OS= 95.8 vs. 74.5%, P = 0.045 DFS=89.1 vs. 70.4%, P = 0.027 LRFS =97.7 vs. 78.7%, P = 0.006	ND	Comparable toxicity for Grades 3–4 early side effects: skin reaction, diarrhea, stomatitis, and nausea/ emesis, with the only exception of a higher hematotoxicity rate for the CRT+RHT group (66 vs. 43%, P= 0.032).

RT = radiotherapy, RHT = hyperthermia, OS = overall survival, SR = survival rate, Clinical benefit = complete response + partial response + stable disease, CHT = chemotherapy, DFS = Disease free survival, CRT = chemoradiotherapy, LRFS = local relapse-free survival, ND = not specified

Neoadjuvant CRT in association with RHT and mEHT does not increase toxicity and allows to achieve encouraging results in terms of tumor response and survival in the rectal, colon, and anal cancer patients. Further randomized studies are required to confirm these data.

Pancreatic cancer

Pancreatic cancer has a poor prognosis with a 5-year OS < 10%. This may be because pancreatic cancer is quite resistant to RT and CHT because of its hypoxic microenvironment that diminishes sensitivity to these therapies [50]. Most used CHT schedules include gemcitabine-based regimes, nab-paclitaxel, and for fit patients, the FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) [51], [52]. These drugs, however, have high toxicity and often low efficacy. For this reason, the association of RTH to conventional CHT and RHT has also been introduced for pancreatic cancer treatment, enhancing the drug delivery and diffusion inside the tumor, improving blood flow, reducing hypoxia, and inhibiting DNA repair, hence enhancing tumor apoptosis.

Three studies compared the survival of locally advanced pancreatic cancer after treatment with the combination of CRT and RHT versus CRT alone. Their results show that the addition of RHT increased significantly the survival: OS=8.8 vs. 4.9 months (p = 0.02), OS= 15 vs 11 months (p = 0.025), 1 year OS=80% vs 57% (p=0.021) and PFS=18.6 vs. 9.6 months (p = 0.01) (table 3) [53], [54], [55].

The association of CHT to RHT also results in encouraging survival: median OS of 12.9 -17.7 months, 1 year OS=41%, and 2 years OS=15% [56], [57], [58]. As concerning the tumor response of locally advanced pancreatic carcinoma, the association of CHT to RHT resulted in DCR of 50-61%, [58]. The treatment is well tolerated with a toxicity of G2 pain and a skin rash, and 5% grade III-IV toxicity [54], [58].

A significant increase in survival is also observed when CRT is associated with mEHT than CRT alone, as reported by Fiorentini et al. (OS= 18.0 vs. 10.9 months, p<0.001) [26]. The other two studies report similar survivals on mEHT to treat locally advanced pancreatic carcinoma, OS of 8.9-15.8 months and PFS of 3.9-12.9 months [59], [60]. mEHT also shows high tumor response in locally advanced pancreatic carcinoma with DCR of 71-96% and safety without grade III-IV toxicity [26], [59]. These better tumor response and survival results of CHT and/or RT in association with mEHT are also observed in geriatric (>65 years) patients with pancreatic cancer. Indeed, a greater DCR, OS, and PFS are reported for the mEHT group and no-mEHT group in this population (table 3) [61].

Table 3) Locally advanced pancreatic cancer

Author	Year	Treatment	Hyperthermia protocol	No. of Pts. (n)	Survival	Tumor Response	RHT related toxicity
Sarti [61]	2020	mEHT+RT or CHT with gemcitabine regimen vs RT or CHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	32	OS= 18 months (range 10.3-28.6) versus 10.97 months (range 4.00-22.16) PFS=12 months (range 3-28.6) versus 4.53 months (range 1.33-17.57) (p=0.003)	DCR= 85% vs 26% (p=0.0018).	3% of G1-G2 skin pain and burns
Fiorentini [26]	2019	mEHT+RT or CHT with gemcitabine regimen vs RT or CHT	mEHT with 13.56 MHz (EHY-2000) twice a week (8 times)	106	OS= 18.0 months vs 10.9 months (p<0.001)	3 months DCR= 92% vs 66%	no grade III–IV toxicity
Iyikesici [60]	2019	CHT with gemcitabine or FOLFIRINOX regimen +mEHT	mEHT with 13.56 MHz (EHY-3010) at 110-130W power for 60 minutes	25	OS=15.8 months (95% CI, 10.5–21.1) PFS=12.9 months (95% CI, 11.2–14.6)	3 months DCR=96%	None
Ono [56]	2019	CHT with FOLFIRINOX, Gemsitabin plus nab-Pacritaxel or S-1 +RHT	RHT with Thermotron RF-8, for 50 minutes after CHT once a week (5 times)	28	1 year OS=41% 2 years OS=15%	3 months DCR=57% 6 months DCR=45% 12 months DCR=12% 18 months DCR=6%	ND

Author	Year	Treatment	Hyperthermia protocol	No. of Pts. (n)	Survival	Tumor Response	RHT related toxicity
Maebayashi [53]	2017	CRT with 5-fluororuracil or gemcitabine + RHT vs CRT	RHT with Thermotron RF-8, for 50 minutes at 800-1200W power once or twice a week (5 times)	13	1 year OS=80% vs 57% (p=0.021)		Lower hematological and gastrointestinal toxicity than CRT alone
Tschoep-Lechner [57]	2013	CHT with gemcitabine and cisplatin +RHT	RHT with BSD-2000 day 2 and 4, 1 hour twice a week for 4 months	27	PFS = 5.9 months OS 12.9 months	DCR=50%	no grade III–IV toxicity
Maluta [55]	2011	CRT with gemcitabine based regimens+RHT vs CRT	RHT with BSD-2000 Once a week (1-5 times)	68	Median OS= 15 vs 11 months (p = 0.025)		
Volovat [59]	2014	CHT (GEMOX) +mEHT	mEHT with EHY-2000 device at 70-150 W on day 1, 3, 5 of every CHT cycle	26	Median PFS= 3.9 months. Median OS= 8.9 months.	DCR=71%	no grade III–IV toxicity
Ishikawa [58]	2012	CHT with gemcitabine+RHT	RHT with Thermotron RF-8 at 1100 to 1500 W power for 40 minutes once a week	18	Median OS=17.7 months	ORR=11.1% DCR= 61.1%	G2 pain and a skin rash
Ohguri [54]	2008	CRT with gemcitabine+RHT vs CRT	RHT with Thermotron RF-8 at 900W power, once a week 1–3 hours after RT and during CHT	29	Median OS=8.8 vs. 4.9 months, P = 0.02, Median PFS=18.6 vs. 9.6 months, P = 0.01	ND	5% grade III–IV toxicity

RT = radiotherapy, RHT = hyperthermia, OS = overall survival, SR = survival rate, Clinical benefit = complete response + partial response + stable disease, CHT = chemotherapy, DFS = Disease free survival, CRT = chemoradiotherapy, LRFS = local relapse-free survival, DCR = disease control rate, mEHT = modulated electro-hyperthermia, ORR = overall response rate

These data suggest that RHT increases CRT and CHT benefit both in median OS and DCR in locally advanced or metastatic pancreatic cancer with low toxicity. Further studies to investigate CRT and RHT in locally advanced pancreatic cancer include the HEATPAC trial, a phase II randomized trial (62).

Summary

In association with radiotherapy and/or chemotherapy, regional hyperthermia may increase median OS, PFS, and tumor response of patients with esophageal, colon, rectal, anal, and locally advanced or metastatic pancreatic cancer. The mEHT is a relatively new regional hyperthermia method that targets tumor cell membranes and extra matrix tissue to increase cancer tissue temperature and sensitize it to cancer therapies. This method has relatively few published studies. However, the results are interesting and comparable to those of other RHT, amplifying both chemotherapy and radiotherapy's benefits in all the considered tumors and it is well tolerated.

Conclusion

The data presented in this narrative review are from retrospective and prospective studies and suggests that regional hyperthermia in association with radiotherapy and/or chemotherapy may increase median OS, PFS, and tumor response of patients with esophageal, colon, rectal, anal, and locally advanced or metastatic pancreatic cancer. mEHT is a relatively new method of regional hyperthermia that targets tumor cell membranes and extra matrix tissue to increase the temperature inside cancer tissue and sensitize it to cancer therapies. This method has few published studies in gastrointestinal cancers. However, the results are comparable to those of other RHT, amplifying both chemotherapy and radiotherapy's benefits in all the considered tumors and is well tolerated (63).

The studies presented have a heterogeneity as concerning the RHT protocols, for this reason, it is difficult to compare the results of different studies. Standardized RHT protocols and more randomized clinical trials are needed for each tumor type to address this issue.

References

[1] Peeken JC, Vaupel P, Combs SE. Integrating Hyperthermia into Modern Radiation Oncology: What Evidence Is Necessary? Front Oncol. 2017;7:132. [doi:10.3389/fonc.2017.00132]

[2] Sauer R, Creeze H, Hulshof M, Issels R, Ott O; Interdisciplinary Working Group for Clinical Hyperthermia (Atzelsberg Circle) of the German Cancer Society and the German Society of Radiooncology. Concerning the final report "Hyperthermia: a systematic review" of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. Strahlenther Onkol. 2012;188(3):209-13. [doi: 10.1007/s00066-012-0072-9]

[3] Datta NR, Ordóñez SG, Gaipl US, Paulides MM, Crezee H, Gellermann J, et al. Local hyperthermia combined with radiotherapy and-/or chemotherapy: recent advances and promises for the future. Cancer Treat Rev. 2015;41:742-53. [doi: 10.1016/j.ctrv.2015.05.009]

[4] Lee SY, Fiorentini G, Szasz AM, Szigeti G, Szasz A, Minnaar CA. Quo Vadis Oncological Hyperthermia (2020)? Front Oncol. 2020;10:1690. [doi: 10.3389/fonc.2020.01690]

[5] Song CW. Effect of local hyperthermia on blood flow and microenvironment: a review. Cancer Res. 1984;44(10):4721s-4730s. [PMID: 6467226]

[6] Welch HG, Schwartz LM, Woloshin S (2000) Are increasing 5-year survival rates evidence of success against cancer? JAMA 283(22):2975-2978

[7] Morgan G, Ward R, Barton M (2004) The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin Oncol (R Coll Radiol) 16(8):549-560

[8] Bailair JC, Smith EM (1986) Progress against cancer? The New England Journal of Medicine 314(19):1226-1232

[9] Holleb AI (1986) Progress against cancer? A broader view. CA Cancer Journal for Clinicians 36:243-244

[10] Schoenbach VJ (1999) Descriptive studies and surviallence-solutions. www.epidemiolog.net/evolving/DescriptiveStudiesSolns.pdf Cited 12 September 2007

[11] Bailar JC, Gornik HL (1997) Cancer undefeated. The New England Journal of Medicine 336(22):1569-1574

[12] Pauling L (1989) Quoted by Moss RW: The Cancer Syndrome. Equinox Press, New York

[13] Arnold K (2003) Statistics offer insights into progress against cancer. Journal of the National Cancer Institute 95(17):1266-1267

[14] Parmar G, Rurak E, Elderfield M, et.al. (2020) 8-year observational study on naturopathic treatment with modulated electro-hyperthermia (mEHT): A single-centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 13, pp.227-266, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[15] Garay T, Kiss E, Szentmartoni Gy, et.al. (2020) Gastrointestinal cancer series treated with modulated electro-hyperthermia (mEHT) – A single centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 8, pp.159-162, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[16] Kim S, Lee JH, Cha J, You SH. (2021) Beneficial effects of modulated electro-hyperthermia during neoadjuvant treatment for locally advanced rectal cancer, Int J Hyperthermia, 38:1, 144-151, DOI: 10.1080/02656736.2021.1877837, https://pubmed.ncbi.nlm.nih.gov/33557636/

[17] Kim J-H, Kim M-Y, Kim H-Y. (2019): Potential Application of Neoadjuvant Chemotherapy Plus Modulated Electrohyperthermia (mEHT, trade name: Oncothermia) Among Patients with Advanced Cancer: Retrospective Clinical Analysis of Single Hospital Experiences, Oncothermia Journal 27: 62-75, www.oncotherm.com/sites/oncotherm/files/2019-10/Potential_Application_of_Neoadjuvant.pdf

[18] Hager ED, Dziambor H, Höhmann D, et al. (1999) Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Res 19(4C):3403–3408, http://www.ncbi.nlm.nih.gov/pubmed/10629627

[19] Douwes FR. (2006) Thermochemotherapy of the advanced pancreas carcinoma. Biologische Medizin 35:126–130, https://www.researchgate.net/publication/287861898_Thermo-chemotherapy_of_the_advanced_pancreas_carcinoma

[20] Douwes F. (2018): Therapy of advanced, therapy resistant pancreas cancer, with local hyperthermia in combination with chemotherapy; Oncothermia Journal 24:91-108, https://oncotherm.com/sites/oncotherm/files/2018-10/Therapy_of_advanced.pdf

[21] Dani A, Varkonyi A, Magyar T, Szasz A (2008) Clinical study for advanced pancreas cancer treated by oncothermia. Forum Hyperthermie 1:13–20, http://www.pyatthealth.com/wp-content/uploads/2015/03/Hyperthermia-Pancreatic-Cancer.pdf

[22] Turner PF, Schaefermeyer T. Technical Aspects of Hyperthermia. In: Issels RD, Wilmanns W. (eds) Application of Hyperthermia in the Treatment of Cancer. Recent Results in Cancer Research. Springer, Berlin, Heidelberg. 1988;107. [https://doi.org/10.1007/978-3-642-83260-4_10]
[23] Kelleher DK, Thews O, Rzeznik J, Scherz A, Salomon Y, Vaupel P. Water-filtered infrared-A radiation: a novel technique for localized hyperthermia in combination with bacteriochlorophyll-based photodynamic therapy. Int J Hyperthermia. 1999;15(6):467-74. [doi: 10.1080/026567399285468]
[24] Kok HP, Crezee J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. Int J Hyperthermia. 2017;33(4):378-386. [doi: 10.1080/02656736.2016.1268726]
[25] Szasz AM, Minnaar CA, Szentmártoni G, Szigeti GP, Dank M. Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) Method: An Update for the Practicing Oncologist. Front Oncol. 2019;9:1012. [doi: 10.3389/fonc.2019.01012]
[26] Fiorentini G, Sarti D, Casadei V, Milandri C, Dentico P, Mambrini A, Nani R, Fiorentini C, Guadagni S. Modulated Electro-Hyperthermia as Palliative Treatment for Pancreatic Cancer: A Retrospective Observational Study on 106 Patients. Integr Cancer Ther. 2019;18:1534735419878505. [doi: 10.1177/1534735419878505].
[27] Forika G, Balogh A, Vancsik T, Zalatnai A, Petovari G, Benyo Z, Krenacs T. Modulated Electro-Hyperthermia Resolves Radioresistance of Panc1 Pancreas Adenocarcinoma and Promotes DNA Damage and Apoptosis In Vitro. Int J Mol Sci. 2020; 21(14):5100 [https://doi.org/10.3390/ijms21145100]
[28] Vancsik T, Forika G, Balogh A, Kiss E, Krenacs T. Modulated electro-hyperthermia induced p53 driven apoptosis and cell cycle arrest additively support doxorubicin chemotherapy of colorectal cancer in vitro. Cancer Med. 2019;8(9):4292-4303. doi: 10.1002/cam4.2330. Epub 2019 Jun 10. [PMID: 31183995; PMCID: PMC6675742]
[29] Nishimura S, Saeki H, Nakanoko T, Kasagi Y, Tsuda Y, Zaitsu Y, Ando K, Nakashima Y, Imamura YU, Ohgaki K, Oki E, Ohga S, Nakamura K, Morita M, Maehara Y. Hyperthermia combined with chemotherapy for patients with residual or recurrent oesophageal cancer after definitive chemoradiotherapy. Anticancer Res. 2015;35(4):2299-303. [PMID: 25862892]
[30] Hu Y, Li Z, Mi DH, Cao N, Zu SW, Wen ZZ, Yu XL, Qu Y. Chemoradiation combined with regional hyperthermia for advanced oesophageal cancer: a systematic review and meta-analysis. J Clin Pharm Ther. 2017;42(2):155-164. [doi:10.1111/jcpt.12498]
[31] Albregts M, Hulshof MC, Zum Vörde Sive Vörding PJ, van Lanschot JJ, Richel DJ, Crezee H, Fockens P, van Dijk JD, González González D. A feasibility study in oesophageal carcinoma using deep loco-regional hyperthermia combined with concurrent chemotherapy followed by surgery. Int J Hyperthermia.
[32] Nakajima M, Kato H, Sakai M, Sano A, Miyazaki T, Sohda M, Inose T, Tanaka N, Suzuki S, Masuda N, Fukuchi M, Kuwano H. Planned Esophagectomy after Neoadjuvant Hyperthermo-Chemoradiotherapy using Weekly Low-Dose Docetaxel and Hyperthermia for Advanced Esophageal Carcinomas. Hepatogastroenterology. 2015;62(140):887-91 [PMID: 26902022]
[33] Hulshof MC, Van Haaren PM, Van Lanschot JJ, Richel DJ, Fockens P, Oldenborg S, Geijsen ED, Van Berge Henegouwen MI, Crezee J. Preoperative chemoradiation combined with regional hyperthermia for patients with resectable esophageal cancer. Int J Hyperthermia. 2009;25(1):79-85 [doi: 10.1080/02656730802464078]
[34] Sheng L, Ji Y, Wu Q, Du X. Regional hyperthermia combined with radiotherapy for esophageal squamous cell carcinoma with supraclavicular lymph node metastasis. Oncotarget. 2017;8(3):5339-5348. [doi:10.18632/oncotarget.14148]
[35] Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-164. [doi: 10.3322/caac.21601]
[36] De Haas-Kock DFM, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, Mastrigt GAV, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database Syst Rev 2009;3:CD006269. [doi: 10.1002/14651858.CD006269.pub2]
[37] Elming PB, Sørensen BS, Oei AL, Franken NAP, Crezee J, Overgaard J, Horsman MR. Hyperthermia: The Optimal Treatment to Overcome Radiation Resistant Hypoxia. Cancers (Basel). 2019;11(1):60. [doi:10.3390/cancers11010060]
[38] Gani C, Schroeder C, Heinrich V, Spillner P, Lamprecht U, Berger B, Zips D. Long-term local control and survival after preoperative radiochemotherapy in combination with deep regional hyperthermia in locally advanced rectal cancer. Int J Hyperthermia. 2016;32(2):187-92. doi: 10.3109/02656736.2015.1117661. Epub 2016 Jan 11.PMID: 26754458

[39] Zwirner K, Bonomo P, Lamprecht U, Zips D, Gani C. External validation of a rectal cancer outcome prediction model with a cohort of patients treated with preoperative radiochemotherapy and deep regional hyperthermia. Int J Hyperthermia. 2018;34(4):455-460. [doi: 10.1080/02656736.2017.1338364]
[40] Maluta S, Romano M, Dall'oglio S, Genna M, Oliani C, Pioli F, Gabbani M, Marciai N, Palazzi M. Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum. Int J Hyperthermia. 2010;26(2):108-17. [doi: 10.3109/02656730903333958]
[41] Rau B, Wust P, Tilly W, Gellermann J, Harder C, Riess H, Budach V, Felix R, Schlag PM. Preoperative radiochemotherapy in locally advanced or recurrent rectal cancer: regional radiofrequency hyperthermia correlates with clinical parameters. Int J Radiat Oncol Biol Phys. 2000;48(2):381-91. [doi: 10.1016/s0360-3016(00)00650-7]
[42] Ott OJ, Schmidt M, Semrau S, Strnad V, Matzel KE, Schneider I, Raptis D, Uter W, Grützmann R, Fietkau R. Chemoradiotherapy with and without deep regional hyperthermia for squamous cell carcinoma of the anus. Strahlenther Onkol. 2019;195(7):607-614. [doi: 10.1007/s00066-018-1396-x]
[43] Shoji H, Motegi M, Osawa K, Okonogi N, Okazaki A, Andou Y, Asao T, Kuwano H, Takahashi T, Ogoshi K. A novel strategy of radiofrequency hyperthermia (neothermia) in combination with preoperative chemoradiotherapy for the treatment of advanced rectal cancer: a pilot study. Cancer Med. 2015;4(6):834-43. [doi: 10.1002/cam4.431]
[44] Kato T, Fujii T, Ide M, Takada T, Sutoh T, Morita H, Yajima R, Yamaguchi S, Tsutsumi S, Asao T, Oyama T, Kuwano H. Effect of long interval between hyperthermochemoradiation therapy and surgery for rectal cancer on apoptosis, proliferation and tumor response. Anticancer Res. 2014;34(6):3141-6. [PMID: 24922685]
[45] Schroeder C, Gani C, Lamprecht U, von Weyhern CH, Weinmann M, Bamberg M, Berger B. Pathological complete response and sphincter-sparing surgery after neoadjuvant radiochemotherapy with regional hyperthermia for locally advanced rectal cancer compared with radiochemotherapy alone. Int J Hyperthermia. 2012;28(8):707-14. [doi: 10.3109/02656736.2012.722263]
[46] Tsutsumi S, Tabe Y, Fujii T, Yamaguchi S, Suto T, Yajima R, Morita H, Kato T, Shioya M, Saito J, Asao T, Nakano T, Kuwano H. Tumor response and negative distal resection margins of rectal cancer after hyperthermochemoradiation therapy. Anticancer Res. 2011;31(11):3963-7. [PMID: 22110227]
[47] Kang MK, Kim MS, Kim JH. Clinical outcomes of mild hyperthermia for locally advanced rectal cancer treated with preoperative radiochemotherapy. Int J Hyperthermia. 2011;27(5):482-90. [doi: 10.3109/02656736.2011.563769]
[48] You SH, Kim S. Feasibility of modulated electro-hyperthermia in preoperative treatment for locally advanced rectal cancer: Early phase 2 clinical results. Neoplasma. 2020;67(3):677-683. [doi: 10.4149/neo_2020_190623N538]
[49] Ranieri G, Laface C, Laforgia M, De Summa S, Porcelli M, Macina F, Ammendola M, Molinari P, Lauletta G, Di Palo A, Rubini G, Ferrari C, Gadaleta CD. Bevacizumab Plus FOLFOX-4 Combined With Deep Electro-Hyperthermia as First-line Therapy in Metastatic Colon Cancer: A Pilot Study. Front Oncol. 2020;10:590707. [doi: 10.3389/fonc.2020.590707]
[50] van der Horst A, Versteijne E, Besselink MGH, Daams JG, Bulle EB, Bijlsma MF, Wilmink JW, van Delden OM, van Hooft JE, Franken NAP, van Laarhoven HWM, Crezee J, van Tienhoven G. The clinical benefit of hyperthermia in pancreatic cancer: a systematic review. Int J Hyperthermia. 2018;34:969-979. [doi: 10.1080/02656736.2017.1401126.]
[51] Liu X, Yang X, Zhou G, Chen Y, Li C, Wang X. Gemcitabine based regional intra-arterial infusion chemotherapy in patients with advanced pancreatic adenocarcinoma. Medicine (Baltimore). 2016;95:e3098. [doi: 10.1097/MD.0000000000003098]
[52] Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, El-Rayes BF, Wang-Gillam A, Lacy J, Hosein PJ, Moorcraft SY, Conroy T, Hohla F, Allen P, Taieb J, Hong TS, Shridhar R, Chau I, van Eijck CH, Koerkamp BG. A patient-level meta analysis of FOLFIRINOX for locally advanced pancreatic cancer. Lancet Oncol. 2016;17:801-810. [doi: 10.1016/S1470-2045(16)00172-8]
[53] Maebayashi T, Ishibashi N, Aizawa T, Sakaguchi M, Sato T, Kawamori J, Tanaka Y. Treatment outcomes of concurrent hyperthermia and chemoradiotherapy for pancreatic cancer: Insights into the significance of hyperthermia treatment. Oncol Lett. 2017;13(6):4959-4964. [doi: 10.3892/ol.2017.6066]
[54] Ohguri T, Imada H, Yahara K, Morioka·T, Nakano K,·Korogi Y. Concurrent chemoradiotherapy with gemcitabine plus regional hyperthermia for locally advanced pancreatic carcinoma: initial experience. Radiat Med. 2008;26:587-596. [DOI 10.1007/s11604-008-0279-y]

[55] Maluta S, Schaffer M, Pioli F, Dall'oglio S, Pasetto S, Schaffer PM, Weber B, Giri MG. Regional hyperthermia combined with chemoradiotherapy in primary or recurrent locally advanced pancreatic cancer: an open-label comparative cohort trial. Strahlenther Onkol. 2011;187(10):619-25. [doi: 10.1007/s00066-011-2226-6]
[56] Ono E, Yano M, Ohshiro T, Shishida M, Sumitani D,Yuzou ,Okamoto Y, Och M. Effectiveness of hyperthermia in clinical stage IV pancreatic cancer. Oncothermia Journal. 2019;27:88-93 [https://oncotherm.com/sites/oncotherm/files/2019-10/Effectiveness_of_hyperthermia.pdf]
[57] Tschoep-Lechner KE, Milani V, Berger F, Dieterle N, Abdel-Rahman S, Salat C, Issels RD. Gemcitabine and cisplatin combined with regional hyperthermia as second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer. Int J Hyperthermia. 2013;29(1):8-16. [doi: 10.3109/02656736.2012.740764]
[58] Ishikawa T, Kokura S, Sakamoto N, Ando T, Imamoto E, Hattori T, Oyamada H, Yoshinami N, Sakamoto M, Kitagawa K, Okumura Y, Yoshida N, Kamada K, Katada K, Uchiyama K, Handa O, Takagi T, Yasuda H, Sakagami J, Konishi H, Yagi N, Naito Y, Yoshikawa T. Phase II trial of combined regional hyperthermia and gemcitabine for locally advanced or metastatic pancreatic cancer. Int J Hyperthermia. 2012;28(7):597-604. [doi: 10.3109/02656736.2012.695428]
[59] Volovat C, Volovat SR, Scripcaru V, Miron L. Second-line chemotherapy with gemcitabine and oxaliplatin in combination with loco-regional hyperthermia (EHY-2000) in patients with refractory metastatic pancreatic cancer—preliminary results of a prospective trial. Rom Rep Phys. 2014;66:166-174 [http://rrp.infim.ro/2014_66_1/A18.pdf]
[60] Iyikesici MS. Long-Term Survival Outcomes of Metabolically Supported Chemotherapy with Gemcitabine-Based or FOLFIRINOX Regimen Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy in Metastatic Pancreatic Cancer. Complement Med Res. 2020;27(1):31-39. [doi: 10.1159/000502135]
[61] Sarti D, Milandri C, Fiorentini C, Mambrini A, Fiorentini G Modulated electro-hyperthermia for the treatment of elderly pancreatic cancer patients. Arguments of Geriatric Oncology. 2020;5(1):1 – 7. [https://www.edisciences.org/scheda-d027]
[62] Datta NP, Pestalozzi B, Clavien PA, Members of the HEATPAC Trial Group. "HEATPAC"—a phase II randomized study of concurrent thermochemoradiotherapy versus chemoradiotherapy alone in locally advanced pancreatic cancer. Radiat Oncol. 2017;12:183. [DOI 10.1186/s13014-017-0923-8]
[63] Minnaar CA, Szasz AM, Arrojo E, Lee S-Y, Fiorentini G, Borbenyi E, Pang CLK, Dank M. Summary and update of the method modulated electrohyperthermia, Oncothermia Journal Special Edition. 2020,2:49-130. [https://oncotherm.com/sites/oncotherm/files/2020-09/specialedition02.pdf]

Addition of Multimodal Immunotherapy to Combination Treatment Strategies for Children with DIPG: A Single Institution Experience

Stefaan W. Van Gool[1], Jennifer Makalowski[1], Erin R. Bonner[2,3], Oliver Feyen [4], Matthias P. Domogalla [1], Lothar Prix [5], Volker Schirrmacher[1], Javad Nazarian[6] and Wilfried Stuecker[1]

[1]Immun-Onkologisches Zentrum Köln
Köln, Germany
[2]Center for Genetic Medicine, Children's National Health System,
Washington, D.C., USA
[3]Institute for Biomedical Sciences,
The GeorgeWashington University School of Medicine and health Sciences,
Washington, D.C., USA
[4]Zyagnum,
Pfungstadt, Germany
[5]Biofocus,
Recklinghausen, Germany
[6]DIPG Research Institute, Universitäts-Kinderspital Zürich,
Zürich, Switzerland

Citation: Van Gool S. W. et al. (2020): Addition of Multimodal Immunotherapy to Combination Treatment Strategies for Children with DIPG: A Single Institution Experience, Oncothermia Journal 30: 37 – 53,

Reprinted from: https://www.mdpi.com/2305-6320/7/5/29
http://www.oncotherm.com/sites/oncotherm/files/2021-04/VanGool_Addition.pdf