Updates of the application of Regional Hyperthermia in the treatment of esophageal, colorectal and pancreatic cancers.

Regional Hyperthermia for gastrointestinal cancers treatment

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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) and radiotherapy (RT) and chemoradiotherapy (CRT) and immunotherapy, enhancing their benefit, also in the treatment of gastrointestinal tumor: esophageal, colorectal and pancreatic cancer. However, RHT has not yet become a common therapy in everyday 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 tumors sensitization, notwithstanding the thickness of the adipose tissue, 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 settings in esophageal, colorectal and pancreatic cancer. This article summarizes the available data of RHT for these tumors.

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

Core tip

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. The 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 relatively few published studies, however, the results are exciting and comparable to those of other RHT, amplifying the benefits of both chemotherapy and radiotherapy in all the considered tumors and is well tolerated.

Introduction

Regional hyperthermia (RHT) efficacy in the remission of malignant tumors has been known for decades. RHT is achieved by increasing the tissue/body temperature with an external electromagnetic field with rapid fields alterations. Technological developments for local/locoregional heat application allowed RHT to be safe and available for clinical application, showing the beneficial effects of mild RHT (39.5–43°C) and optimizing the devices 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, only a few centers have included this adjuvant treatment in their clinical practice [1].

The basic biological rationale of heat utilization is the enhancement of radiation, chemotherapeutic agents, and immunotherapy effects, allowing radiation dose reduction. Heat triggers changes in tumor perfusion and oxygenation, inhibition of DNA repair mechanisms and immune stimulation by exposing tumor antigens [1, 2]. Indeed, local radiotherapy in association with RHT increases tumor immunogenicity and results in systemic effects 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 tumors sensitization, notwithstanding the thickness of the adipose tissue, and overcoming the issue of homogenous heating. The association 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 [3-5].

This is a narrative review aiming to update the current knowledge on RHT use in association with RT and/or CHT in treating esophageal, colorectal and pancreatic cancers.

Types of hyperthermia

There are different types of hyperthermia: superficial hyperthermia, deep/regional hyperthermia, whole-body hyperthermia, interstitial hyperthermia and body orifice insertion hyperthermia [6].

Whole-body hyperthermia increases the entire body's temperature up to a maximum of 41.8°C, using thermal conduction or radiant light techniques. Interstitial hyperthermia places heating electromagnetic devices (needles or catheters) directly inside the tumor. Most interstitial hyperthermia has involved the heating technique. The main advantage of this therapy is that the heating occurs directly inside the tumor, enabling it to reach higher local tumor temperatures than in the surrounding host tissues. Similarly, hyperthermia can be achieved by inserting heating devices into natural body orifices with tumors (body orifice insertion hyperthermia) [6]. Deep/regional hyperthermia can increase the temperature of a portion of the body (at the tumor site) up to a depth of > 5 cm with electromagnetic fields, minimizing the heating of the surrounding tissue [6].

Superficial hyperthermia heats tissues <5cm in depth from the body's surface, using electromagnetic fields. The variability of the blood flow within the treated region also contributes to the temperature variation within the tumor region in all types of hyperthermia, [6].

Regional Hyperthermia

Different methods are used for regional hyperthermia, such as using infrared-A, radiative, capacitive or modulated electro-hyperthermia techniques.

Both radiative and capacitive systems are used for superficial hyperthermia to tumors infiltrating up to 4 cm into the tissue, such as melanoma [7]. Two electrodes are positioned on opposite sides of the body and the electric current flowing between them heats the tissues. The electrodes are placed in direct contact with tumor tissue through a water bolus.

There are several types of commercially available radiative superficial systems, including flexible microwave applicators. They all heat with frequencies of 434 to 915 MHz and are positioned directly in contact with the patient's surface over the targeted tumor [7]. Both methods allow homogeneous heating of the target, but the created hot spots could limit the heating. Radiative heating yields more favorable temperature distribution than capacitive heating does, especially within heterogeneous tissues [7].

The water filter infrared-A radiation method uses a light source (halogen lamp at 24 V/150W) and a water filter built-in as a closed cuvette and absorbs the energy, avoiding painful sensations and burns of the skins [8].

Modulated electro-hyperthermia

Tumor blood flow increase is rather limited upon heating; hence, the heat dissipation is slower than in normal tissues. This is the reason why tumor temperature rises higher than that in normal tissue during hyperthermia [3]. However, the homogenous heating of a tumor to a specified temperature is quite challenging due to the heterogeneous distribution of vasculature inside malignant tissue. Indeed, 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].

To improve the results and reduce the adverse effects of thermal therapy, a new method has been recently developed: the modulated electro-hyperthermia (mEHT) [9]. This method targets malignant cell membranes and the extracellular matrix. This allows sensitizing deep tumors, notwithstanding the thickness of the adipose tissue, and overcoming the issue of homogenous heating [9].

mEHT is performed using a 13.56 MHz capacitive coupled device (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 [9-13]. Hyperthermia is achieved by applying short radio-frequency waves of 13.56 MHz with capacitive coupling to increase tumor temperature to 41.5°C for >90% of treatment duration [10].

Literature search

This narrative review analyses the relevant professional literature searched in prestigious databases as PubMed-MEDLINE, Embase, Cochrane and ClinicalTrials.gov. The chosen search terms: hyperthermia, pancreatic, gastrointestinal, esophageal, colon, rectal, colorectal, anal cancer. The search had collected 934 papers. In further selection, the review includes only full-text manuscripts in the English language, articles reporting results from an observational or experimental trial that had tumor response, survival or progression-free survival or toxicity among their outcomes were registered, and it was published in years 2000 - 2020. The selection did choose 38 manuscripts and was divided according to tumor type. In the further selection, we kept

only the original manuscript (25) and collected with reference tables in three groups of cancers: esophageal, colorectal and pancreatic.

Esophageal Cancer

The prognosis of esophageal cancer remains poor and long-term survival after potentially curative surgery is 5–20% [14, 15]. Several studies on neo-adjuvant chemotherapy alone fail to prove the benefit of this preoperative treatment, however, promising results have been achieved with the combination of heat and chemotherapy in this setting [15-18].

Neoadjuvant chemotherapy (NCHT) or chemoradiotherapy (CRT) in combination with RHT have positive results concerning survival and tumor response of esophageal cancer patients (table 1). 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 [18].

A phase II study with chemotherapy (carboplatin and paclitaxel) and radiotherapy associated with RHT as neo-adjuvant treatment provide good locoregional control and overall survival for esophageal cancer patients who 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 and survival rates at 1, 2 and 3 years are 79%, 57% and 54% respectively. Quality of life is good for these patients and the toxicity is low [17]. Similar results in survival are reported by another phase I/II study, showing 1- and 2-year survival rates of 69 and 62%, respectively [15].

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 a low toxicity and excellent local control of esophageal cancer with supraclavicular lymph node metastasis [18].

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 overall survival (OS) of esophageal cancer patients; decreased both recurrence, distant metastases and gastrointestinal reaction rates [14]. These results deliver evidence of CRT+RHT benefits in esophageal cancer neoadjuvant therapy. The pieces of evidence base very hopeful expectations; however, further randomized clinical studies 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 and is the second most common cause of cancer death in the United States [19]. In the past decades, neoadjuvant radiotherapy alone or in association with chemotherapy followed by surgery has become a standard treatment for advanced rectal cancer [20]. CHT is used to enhance the RT effects of radiotherapy. RHT is another method to amplify radiotherapy, overcoming the low oxygen concentrations present in large tumors and hamper the effect of radiotherapy. RHT, indeed, increases the tumor blood flow and hence the tissue oxygenation [21].

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 [22]. 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 [23-25]. In particular, a study compares OS of CRT alone or in association with

RHT and reports that the combined therapy allows longer OS than CRT alone (5 years OS=76% versus 88% p < 0.08) [22]. This improvement in survival is also observed when the neoadjuvant CRT and RHT is performed for anal cancer treatment with five years OS (95.8 vs. 74.5%, P = 0.045), disease-free survival (DFS=89.1 vs. 70.4%, P = 0.027) and local relapse-free survival (LRFS =97.7 vs. 78.7%, P = 0.006) more favorable than CRT alone [26].

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) [27-31]. 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 [27-31].

mEHT in association with CHT is used in a study to treat metastatic colon cancer patients with reasonable 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) [32]. Another study applies mEHT in association to CRT for the treatment of rectal cancer patients, reporting minimal, moderate, near-total, and total regression of primary tumor of 15.0%, 51.7%, 18.3% and 15.0%, respectively [33]. The mEHT is well tolerated in both studies, with predominantly mild hyperthermia toxicity [32, 33].

Neoadjuvant CRT in association with RHT and mEHT does not increase toxicity and allows to achieve encouraging results in terms of both tumor response and survival in rectal, colon and anal cancers 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 due to the fact that pancreatic cancer is quite resistant to RT and CHT, because of its hypoxic microenvironment that diminishes sensitivity these therapies [34]. Most used CHT schedules include gemcitabine-based regimes, nab-paclitaxel and for fit patients, the FOLFIRINOX (leucovorin, fluorouracil, irinotecan and oxaliplatin) [35, 36]. 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 [34].

Three studies compared the survival of locally advanced pancreatic cancer after treatment with the combination 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) [37-39]. The association of CHT to RHT also encourages survival: median OS of 12.9 -17.7 months, 1 year OS=41% and two years OS=15% [40-42]. As concerning the tumor response of locally advanced pancreatic carcinoma, the association of CHT to RHT resulted in a DCR of 50-61% [40, 42]. The treatment is well-tolerated with toxicity of G2 pain and a skin rash and 5% grade III–IV toxicity [38, 42].

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) [10]. The other two studies report similar survivals on mEHT for locally advanced pancreatic carcinoma treatment, OS of 8.9-15.8 months and PFS of 3.9-12.9 months [43, 44]. mEHT also shows a high tumor response in locally advanced pancreatic carcinoma with DCR of 71-96% and safety without grade III-IV toxicity [10, 43, 44]. These better tumor response and survival results of CHT and/or RT in association with mEHT are also observed in aged (>65 years) patients with pancreatic cancer, indeed, a greater DCR, OS and PFS are reported for mEHT group and no-mEHT group in this population (table 3) [45].

These data suggest that RHT increases CRT and CHT benefit both in terms of median OS and in DCR in locally advanced or metastatic pancreatic cancer with low toxicity. Further studies investigating CRT and RHT in locally advanced pancreatic cancer include the HEATPAC trial, a phase II randomized trial (46).

Conclusions

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 extracellular matrix of the cancerous 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 the benefits of both chemotherapy and radiotherapy in all the considered tumors and is well tolerated (47).

The studies presented have heterogeneity concerning the RHT protocols. For this reason it is challenging 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.

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Conflict-of-interest

The authors have no conflict of interest

Table 1) Esophageal cancer

Author	*Year*	*Treatment*	*Hypertermia protocol*	*Number of patients (n)*	*Survival*	*Tumor Response*	*RHT related toxicity*
Sheng [18]	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 [13]	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 [16]	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 [17]	2009	Neoadjuvant CRT with carboplatin and paclitaxel+ RHT	home-made AMC (academical medical center), phased array of four 70MHz	28	1 year OS=79% 2 years OS=57%	CR=19% PR=31% SD=23%	pain (sternal or shoulder) or general discomfort in seven

			antennas, at a power of 800 W for 1.5 hour		3 years OS= 54%		patients and in two patients
Albregts [15]	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.

Table 2) Colorectal and anal cancer

Author	Year	Type of tumor	Treatment	Hypertermia protocol	Nr of patients (n)	Survival	Tumor Response	RHT related toxicity
Ranieri [33]	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 [32]	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 [23]	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 [22]	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
Shoji [27]	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 [28]	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
Schroeder [29]	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 [31]	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
Maluta [24]	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 [25]	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 [26]	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 = 0.045DFS=89.1 vs. 70.4%, P = 0.027LRFS =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.

Table 3) Locally advanced pancreatic cancer

Author	*Year*	*Treatment*	*Hypertermia protocol*	*Nr of patients (n)*	*Survival*	*Tumor Response*	*RHT related toxicity*
Sarti [45]	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 [10]	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 [44]	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 [40]	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%	ND

						18 months DCR=6%	
Maebayashi [37]	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 [41]	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 [39]	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 [43]	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 [42]	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 [38]	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