Tumors of the hepato-pancreato-biliary system: can we tame the beast?

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Tumors of the hepato-pancreato-biliary system: can we tame the beast?

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Questions

Adjuvant hyperthermia is beneficial in hepatopancreatobiliary cancers?

What about treatment response, survival, and laboratory and quality of life data?

In this overview, the clinical data on hyperthermia in hepatopancreatobiliary tumors is summarized.

a comprehensive guide to

Yellow Stripey Things

Carpenter Bee
-acts like it's hot shit but can't actually hurt you
-has no concept of what glass is
-lives in your fence
-flies aggressively to try and scare you away

Honeybee
-is the bee that needs help the most
-excellent pollenator
-very friendly
-can only sting once

Bumblebee
-also pollenates stuff very well
-so fat it shouldn't be able to fly
-will let you pet it without getting agitated
-actually a flying panda

Hoverfly
-wears yellow stripey uniform to scare you
-actually can't do anything to you
-hangs out in fields
-follows you if it likes you

Paper Wasp
-looks scary, but will only attack if provoked
-sting hurts like hell
-will chase you if you swat at it
-has no concept of personal space

Yellow Jacket
-wants your food and will fight you for it
-never leaves you alone
-will sting you just for the hell of it
-is just an asshole

Cicada Killer
-looks like Satan's nightmares
-exclusively eats cicadas
-can sting you, but usually won't
-still pretty terrifying

Dirt Dauber
-almost never stings anything except spiders
-builds nest in the ground
-hoards spiders in said nest
-coolest looking of the wasps

In fact... Hepatopancreatobiliary tumors

PANCREAS HEPATOCELLULAR CHOLANGIOCELLULAR

honey bee *bumble bee* *wasp*

https://www.almanac.com/wasps-bees-and-hornets-whats-difference

Hepatopancreatobiliary (HPB) cancers

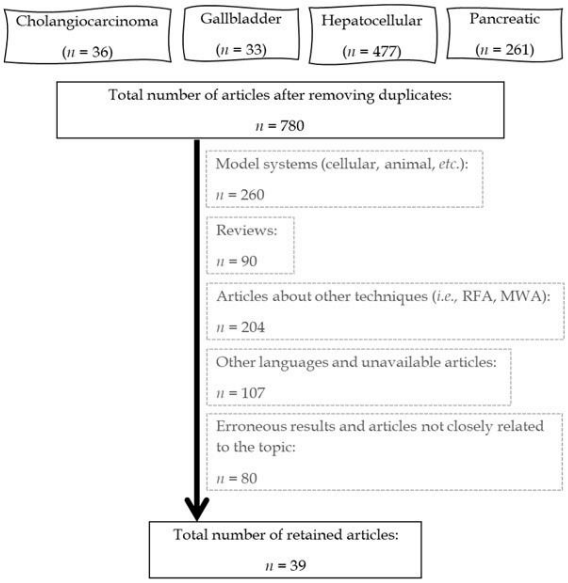
- Fatal diseases that can be characterized by **very low 5-year survival rates**[1-3].
- In 2018, over **1.5 million new cases** and approximately **1.4 million deaths** from hepatocellular (HCC), biliary (BC) including gallbladder and cholangiocellular (CCC), and pancreatic cancers (PC) were reported[4].
- Diagnosis at a **more advanced stage** is characteristic to all four tumor types[1-3], which is usually accompanied by **other comorbidities** like a cirrhotic state of the liver, which further worsens patient life expectancy [1].
- In the last decades**, several new techniques** and possible multimodal therapies have emerged that support conventional surgical resection and facilitate chemoradiotherapy, including but not limited to various thermal ablative methods[5] including radiofrequency[6] and microwave ablation[7], laser-induced thermotherapy[8], hyperthermic intraperitoneal chemotherapy[9], percutaneous ethanol injection[10], transcatheter arterial chemoembolization[11], high-intensity focused ultrasound[12], and various types of hyperthermia[13].
- The available **literature** on the clinical applications of hyperthermia in hepatopancreatobiliary cancers will be discussed focusing on survival and safety data.

Methods

- A literature search was conducted in **PubMed/MEDLINE** using the strings "cholangiocarcinoma hyperthermia", "gallbladder cancer hyperthermia", "hepatocellular hyperthermia", and "pancreatic cancer hyperthermia", for articles published **from January 1, 1964 to January 31, 2021**. After removing duplicates, a total of 780 potential articles were found, from which 39 full-text articles were selected. A secondary search in **ClinicalTrials.gov** was conducted, and an additional three finished and four currently running clinical trials were identified. Five additional studies were included from another search in meta-analysis and review citations, raising the **total number of 47 publications** included in this review.
- Figures were drawn with R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria, 2021) and the R package forestplot (version 1.10.1, Max Gordon and Thomas Lumley, 2020). Data were obtained from eligible articles, and a simple difference in overall survival and disease control rate (the sum of complete or partial response to treatment and stable disease) was calculated from the results of the cohorts with and without hyperthermia.

Flow diagram of the selection of PubMed/Medline articles.

MWA: Microwave ablation;
RFA: Radiofrequency ablation.



Hyperthermia in pancreatic cancer (PC)

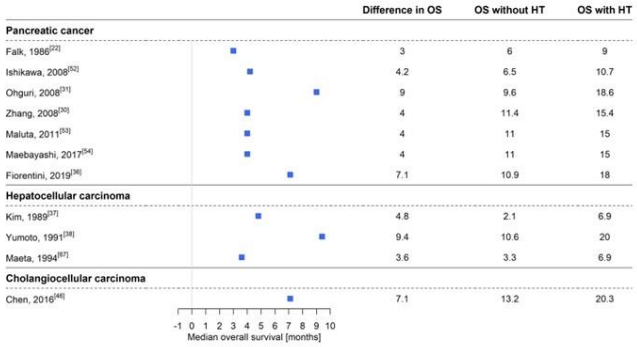
- **Current treatment options** for PC are surgical resection with postoperative chemoradiotherapy, and systemic chemotherapy for borderline resectable and locally advanced or metastatic PCs[3].
- Historically **5-fluorouracil** was the most used chemotherapy agent in advanced and metastatic PCs, but was replaced by **gemcitabine and FOLFIRINOX** (folinic acid + 5-fluorouracil + irinotecan + oxaliplatin) starting in the mid-1990s[48,49].
- **Hyperthermia has been introduced as an auxiliary treatment for advanced and metastatic PCs.**
- **Whole-body hyperthermia** was shown to improve the effect of melphalan on blood cell counts in refractory cancers including PC[26], but no such effect was observed if carboplatin was administered alone[25].
- A treatment regimen of **monthly cisplatin + gemcitabine with whole-body hyperthermia** combined with continuous **low-dose interferon-α** had somewhat improved survival compared with standard chemoradiotherapy in metastatic PC, and a higher partial response rate to thermo-chemotherapy[27].
- In another study, advanced PC patients, who had achieved **partial remission**, had longer median survival than those who had not responded to the treatment (11.4 mo *vs* 15.8 mo)[28].
- A **clinical study (NCT04467593) is currently investigating the effects of whole-body hyperthermia** on current chemotherapy with gemcitabine and FOLFIRINOX[50].

PC cont.

- Several studies demonstrated that **thermo-chemotherapy** of locally advanced or metastatic PCs *via* **regional hyperthermia** had a positive effect on patient survival and therapeutic efficacy. During the last three decades, multiple chemo, radio, and other therapies and procedures were combined with regional hyperthermia in PC[22,23,29-36,47,51-59].
- In detail, **thermo-chemotherapy with selective immune stimulation** resulted in longer patient survival[22].
- In other studies[23,51], patients treated with **chemoradiotherapy and complementary hyperthermia** had **better disease control rates** than those without hyperthermia, **doubling the observed responses** to treatment. Furthermore, the partial response rate increased along with increased maximum output power of the hyperthermia device[51].

Differences in median overall survival between cohorts treated with and without hyperthermia.

HT: Hyperthermia;
OS: Overall survival.



PC cont.

- After the introduction of routine clinical use of **gemcitabine and FOLFIRINOX**, several studies investigated the effect of **regional hyperthermia** on those treatments[29,31-35,47,52-57].
- **Gemcitabine** alone had worse overall survival and treatment response than when used with **complementary hyperthermia**[29,47,52], and better progression-free and overall survival have also been reported with the concomitant use of hyperthermia in combination with radiotherapy[31,53,54].
- The previous observation that **increasing the power output** of the hyperthermia device increases treatment response[51] **was not confirmed** in the case of gemcitabine[31]. **Other chemotherapeutic agents** such as cisplatin[33,34] or oxaliplatin[32] had similar results. Patients in the hyperthermia arm had better partial response rates and better survival than those without hyperthermia.
- In addition, the currently running **HEAT (NCT01077427)[60] and HEATPAC (NCT02439593)[61,62] clinical trials** will further broaden our knowledge of the efficacy and safety of hyperthermia combined with gemcitabine in PC.

PC cont.

- A few case reports have been published recently where chemoradiotherapy and hyperthermia were combined with **herbal remedies**. One German[56] and two Italian[57] reports described treating metastatic PC patients with chemoradiotherapy and hyperthermia supplemented with subcutaneous, fever-inducing **mistletoe** (*Viscum album*) extract and other immunomodulating supplements including **curcumin or shiitake** (*Lentinula edodes*) derivatives. All three patients had survived more than 30 mo with unrestricted quality of life; no deaths were reported at the time of publication[56,57].
- As with conventional regional hyperthermia, positive effects of **mEHT** on progression-free and overall survival, and on improved disease control rate have been observed[36,58]. Metastatic tumors, including PC patients with ascites, have shown better response (absorption of ascites) and quality of life when **mEHT with traditional Chinese herbal remedy** therapy was administered, compared with patients on chemotherapy and regular drainage[59]. A possible correlation between the time from diagnosis to the first mEHT treatment and the survival time from first mEHT treatment was proposed[36].

Hyperthermia in HCC

- **Early-stage HCCs** are treated with surgical resection or liver transplantation, radiofrequency or microwave ablation, or embolization methods with or without chemoradiotherapy.
- **Intermediate and advanced-stage HCCs** are generally treated with systemic and combination therapies[1]. Early studies of **hyperthermia in HCC** investigated the combination of hyperthermia with chemoradiotherapy, transarterial embolization, or transcatheter arterial chemoembolization[23,37-41,63-69]. Significantly longer survival, lower serum alpha-fetoprotein levels, and better response to treatment, even in tumors > 7 cm[23], were observed in those reports[23,37-41,63-69].
- According to the results of one study[64], the best results were achieved if the intratumor **temperature reached > 42 °C**, while in another study[39] **tumors located in the left lobe** of the liver were more responsive to combined treatment with hyperthermia. The latter observation may have resulted from a technical aspect of the treatment, as noted by the authors[39]. In addition to the above, investigations of which treatment option benefits the most from hyperthermia in HCC have found that the best survival and response data have been observed in cases of **immunotherapy with hyperthermia**[41].

HCC cont.

- **Combining** transcatheter arterial chemoembolization, radiotherapy and hyperthermia[43,44], conformal radiotherapy with hyperthermia[20], and mEHT with sorafenib[42] or traditional Chinese herbal remedy therapy[59] were shown to **improve the normalization of laboratory results, disease control rate, progression-free and overall survival, and 1-year recurrence and mortality rates**.
- Results of the **CERT[43,44] study** supplement the above with the following:
  - (1) **radiotherapy related gastroduodenal toxicity** (*e.g.*, ulcers, gastroduodenitis, and others) was significantly **lower** in the hyperthermia cohort; and
  - (2) patients with better tolerance for higher power hyperthermia had the same treatment response rate and survival, suggesting that an **increased power output level did not add to treatment efficacy.**

HCC cont.

- It is known from model systems[70-72] that **heating to fever-range temperatures improves the immune response against tumors, while tumoricidal temperatures (> 42 °C) inhibit host competence.**
- Because of the latter observation, **whole body hyperthermia at tumoricidal temperatures is considered to have an unfavorable effect** on the immune system, while regional hyperthermia does not have this effect, as the tumor-surrounding tissue only heats to fever-like temperatures[70-72].
- Investigation of the $CD4^+$ and $CD8^+$ T, and natural killer (NK) cell immunity after the first treatment and after a whole hyperthermia treatment course in HCC[72] revealed that **antitumoral changes occur in those cells and last up to at least 2 mo**:
  - **NK cells are the first to respond to hyperthermia**. Increased NK cell activity has been observed in patients with below normal or normal levels of pretreatment NK activation. Patients with increased pretreatment NK activity had a slight decrease after treatment, but the difference was not statistically significant.
  - $CD4^+$ **T cell activation** was slightly decreased and $CD8^+$ increased, both after the first and after the complete hyperthermia regimen[72].

Hyperthermia in CCC

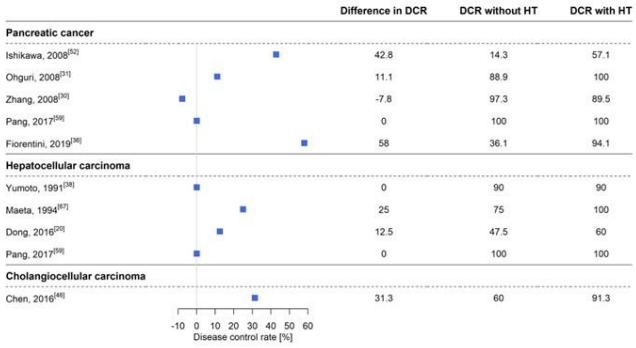
- Of the hepatopancreatobiliary cancers, hyperthermia is the least studied in CCC.
- Conventional **treatment options** of CCC are similar to those of PC and HCC; surgical resection for resectable cases and chemoradiotherapy and systematic combination therapies for advanced and metastatic cases[2].
- Until the mid-2000s no studies had been specifically designed to investigate hyperthermia in CCC.
- The results of studies investigating the effect of hyperthermia on mixed tumor types are available[26,29,41,51,63,64], in which a few biliary cases were also presented.
- **Positive effect of hyperthermia on tumor response rate, tumor markers, and survival have been reported**[26,29,41,51,63,64]; and the **combination of hyperthermia** and transcatheter arterial embolization, chemo- or radiotherapy have been considered as equally good combinations of possible therapies in advanced tumors of the biliary tract[41].

CCC cont.

- **Adjuvant hyperthermia with chemotherapy** has increased the treatment response rate and overall survival of CCC patients[74,75].
- Improvements in **quality of life** (*i.e.* fewer tumor related symptoms) and laboratory results were reported in a detailed case report of a patient with unresectable hilar CCC[75].
- Similarly, extending hepatic arterial infusion chemotherapy with hyperthermia in patients with advanced CCC have resulted in **longer progression-free and overall survival and in better disease control rate**[45,46]. The positive effects of hyperthermia were observed after the first few treatments[46], complete responses have been reported[46], and no increased toxicity after chemotherapy occurred[45].

Differences in the disease control rate between cohorts treated with and without hyperthermia.

DCR: Disease control rate; HT: Hyperthermia.



Core tip

- Adjuvant hyperthermia is beneficial in hepatopancreatobiliary cancers because of its direct and indirect antitumor effects.
- Increased treatment response, prolonged survival, and improved laboratory and quality of life data have been observed in several randomized and observational clinical trials of various hyperthermia methods.
- Regional hyperthermia and mEHT is more advantageous and more accepted among patients than whole-body hyperthermia.
- However, the use of hyperthermia in cancer care is not yet routine.
- A refined or subdivided stage 4 category would be most beneficial to stratify the patients according to tumor load and involved organs, supplemented by serum tumor marker levels.