LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

MEDICINE FACULTY

Isolated Liver Hyperthermic Chemoperfusion: Indications, Technical Considerations, and Results

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TABLE OF CONTENTS

1. SUMMARY

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Title: Indications, technical considerations, and results of isolated liver hyperthermic chemoperfusion: a systematic literature review

Aim: Perform the systematic review of the indications, technical considerations, and results of isolated liver hyperthermic chemoperfusion for cancer patients with unresectable metastatic liver disease.

Methods: This systematic review was designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). A literature search was conducted through PubMed, collecting studies analyzing clinical outcomes of IHP treatment for unresectable liver tumors. Studies were selected according to an inclusion and exclusion criteria, and data was extracted and synthesized.

Results: IHP has shown improvement in patients who have been treated previously with systemic chemotherapy and when used combined as a second line treatment is when the best results have been seen as life expectancy slightly increases.

Conclusion: IHP is a good option as a complimentary treatment when surgical resection of liver tumor metastases is not possible to perform

2. ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to Prof. Žilvinas Dambrauskas for his job behind me, helping me and not letting me down pushing me to work on this research and to not give up.

Also, I must mention my family and friends who gave me the courage to keep working when I had not will to do it and help me to finish this work.

3. ABBREVIATIONS

IHP: Isolated Hepatic Perfusion

CRCLM: colo-rectal cancer liver metastases

ILHC: isolated liver hyperthermic chemoperfusion

GDA: Gastro Duodenal Artery

IVC: Inferior Vena Cava

PIHP: Percutaneous Isolated Hepatic Perfusion

CHA: Common Hepatic Artery

PFS: Progression-free survival

NCI: National Cancer Institute

OS: Overall Survival

PFS*:* Progression-free survival

CHA: common hepatic artery

4. TERMS

Liver: Large, meaty organ that sits on the right side of the belly. The liver's main function is to filter the blood.

Isolated liver hyperthermic chemoperfusion: Chemotherapy technique in which the liver is the main and only objective treated, allowing bigger doses of chemotherapy while decreasing the toxicity in the system.

5. INTRODUCTION

Up to 80% of colorectal, melanoma, and neuroendocrine liver metastases are unresectable because of excessive tumor burden. Isolated hepatic perfusion (IHP) administers intensive therapy to the liver limiting toxicity to the rest of the system and thus may be very beneficial role in the treatment of unresectable liver metastases.

The development of isolated hepatic perfusion (IHP)chemotherapy with temporary isolation from the systemic circulation started in the 1980s. The principle of IHP consists of high dose perfusion of a cytotoxic drug via the hepatic artery and/or the portal vein with the goal of obtaining a maximal anti-tumor effect while limiting systemic toxicity. [1]

Clinical trials using IHP were proposed for selected patients who had unresectable hepatic tumors, mainly colorectal, neuro-endocrine metastases, and melanoma metastases. This technique allows use of high doses of chemotherapy, limited only by hepatic parenchyma tolerance.

Therefore, in this literature review we have studied and carried a guided review of the literature in the past 10 years about the outcomes in treatment, morbidity and survival rates for melanoma metastases, colorectal metastases, and neuroendocrine metastases in the liver by using the isolated hepatic perfusion as treatment.

6. AIM AND OBJECTIVES

Aim:

Perform the systematic review of the indications, technical considerations, and results of isolated liver hyperthermic chemoperfusion for cancer patients with unresectable metastatic liver disease.

Objectives:

1. Overview the technical aspects of the procedure (methodology)
2. Analyze the role of IHP in treatment of melanoma metastases
3. Analyze the role of IHP in treatment colorectal liver metastases
4. Analyze the role of IHP in treatment neuroendocrine liver metastases

7. LITERATURE REVIEW

Liver metastases are a common cause of a variety of malignancies affecting the liver and are often a cause of death in patients suffering it as a result of its difficult treatment. The best treatment for liver tumors would be surgical resection of, preferably, just a portion of the liver. However, just in less than one third of all cases with malignant liver tumors the surgical resection of the liver is a valid option because there would be left a very small piece of liver which would make the liver unfunctional, also because the tumor burdens are big making it so hard to resect or because of other comorbidities which makes impossible to have an optimal surgical intervention. [17]

For these patients where liver resection is not an option, we will have to go for chemotherapy, which is applied systemically with not so big benefit and causing an important toxicity. For this reason, Isolated hepatic perfusion (IHP) has been developed over the past decades as a complex open surgical technique in which the liver is isolated and the perfusion is directed just to the whole liver with high doses of chemotherapy. By isolating the whole vasculature of the liver and its mobilization it is allowed the maximal anti-tumor effect while minimizing the systemic toxicity that would have been done by systemic chemotherapy.

As an alternative approach of IHP obviate a large abdominal operation, and allows repeatable manipulation, which may enable the patients to get maximized therapeutic effects while having a faster recovery. As the management of patients with unresectable liver metastases is still a major problem for physicians, it is still not clear if treating with systemic of IHP if better or if it has more risks than systemic chemotherapy. Here we will study how IHP can be beneficial for these patients. [3]

7.1 Technique of the IHP - how is it performed:

Isolated hepatic perfusion is a technique used to treat the metastases in the liver in a well localized zona and well-focused just on the liver to be able to be more aggressive in the metastasis's zone and more accurate in the zone we want to treat as well as we will reduce the toxicity caused in the rest of the body in the common chemotherapy.

The procedure is started with a deep and conscious examination of the peritoneal cavity and abdomen to evaluate for dissemination or distant lymph node involvement which would be a contraindication to perform this technique in a safe way with a good prognosis. When the lymph nodes that are in the borders of the porta hepatis are resectable, there is no contraindication to perform IHP technique since this has not been proved to affect in an adverse way to the outcome of the treatment.

When there are previous known liver pathologies, such as steatohepatitis, sinusoidal obstructive syndrome, or severe steatosis, are considered as contraindication for IHP. As the objective is to achieve a vascular isolation of the liver, this is obtained by mobilizing the right and left lobes of the liver, at this point, all collateral veins and accessory hepatic arteries of the liver are ligated or clamped. The inferior vena cava (IVC) is exhibited by performing a Kocher maneuver of the duodenum and then all the venous tributaries from the retro hepatic IVC including the right adrenal vein and the phrenic veins are ligated. The structures of the porta hepatis, as the proper hepatic artery, portal vein and common bile duct are completely exposed. The gastroduodenal artery (GDA) is dissected and serves as the cannulation site for prefusion.

The activated clotting time is extremely important during the whole procedure, so that, systemic coagulation is achieved by administering heparin maintaining the activated clotting time of more than 350 seconds. Then, a venous bypass circuit is created from the saphenous vein to the axillary vein to maintain the systemic venous return. This is a key point in the procedure as the flow in the retro hepatic vena cava will be interrupted with occluding clamps during the perfusion. The saphenous vein is canulated with a 12-16 FR catheter using an open or percutaneous insertion technique and the catheter tip is positioned just caudal to the renal veins. A 12-16 Fr catheter is then placed in the axillary vein or internal jugular vein with the tip in the central circulation. These two cannulas are then attached to a centrifugal pump and form the veno-venous bypass circuit.

To stablish the perfusion circuit, vascular clamps are located throughout the intrahepatic IVC above the renal veins just few centimeters apart. Then a venotomy is performed in the IVC between the clamps put previously and there a 20-24 Fr catheter is guided in the retro hepatic vena cava, this catheter is secured with a Romel tourniquet. With this cannula we will achieve venous outflow for the hepatic perfusion circuit. If we can not place the retro hepatic venous cannula, it can be inserted in the femoral vein percutaneously. The common hepatic artery (CHA) and portal vein are also clamped as they have to be occluded because as the main blood supply of the background of the liver arrives from the portal vein, if we don't clamp it, there could be dilution of the chemotherapy and an impairment of the hyperthermia in the circuit. Then, by cannulating the gastro duodenal artery with a 3-4mm arterial catheter with the tip placed at the common hepatic artery orifice, the inflow perfusion circuit will be created. Then a vascular clamp is placed in throughout the suprahepatic vena cava achieving a complete isolation of the liver (Fig. nº1). To finish the preparation of the circuit, to monitor that there is a constant hyperthermic temperature during the whole procedure, two temperatures probes are placed directly into the liver parenchyma on the right and left sides of the liver. Now the perfusion circuit is prepared to start the treatment.

The perfusion circuit consist of a roller pump, membrane oxygenator and a heat exchanger.

The infusion is prepared with 700 ml of balanced salt solution and 1 unit of packed red blood cells, approximately 300 ml. Red blood cells are necessary to make sure that we achieved an adequate oxygenation to the hepatic parenchyma during the perfusion. Blood and arterial gases are constantly monitored throughout the perfusion during the whole to be able to maintain a stable pH between 7.2 and 7.3. This is possible due to de addition of sodium bicarbonate to the infusion.

The heat exchanger is needed to warm the infusion to maintain the hepatic parenchyma at a stable temperature between 38.5 and 40.0 ºC. The optimal flow rate is between 600 to 800 ml/min but a minimum flow over 400 ml/min is ensured. An easy way to see if both lobes are being perfused uniformly is to observe a rapid and uniform increase of temperature in both lobes

The venous outflow reservoir is constantly monitored during the whole procedure to detect changes in volume that could indicate an incomplete vascular isolation of the liver. If this happens, all the vascular clamps must be evaluated, and any other collateral hepatic vessel should be ligated.

The perfusion last 60 minutes and the liver is flushed with 1.5 L. of crystalloids follow by 1.5 L of colloid. Then cannulas are removed, all vascular structures are sutured back together to ensure the normal blood flow and the normal liver perfusion is restored.[2], [6]

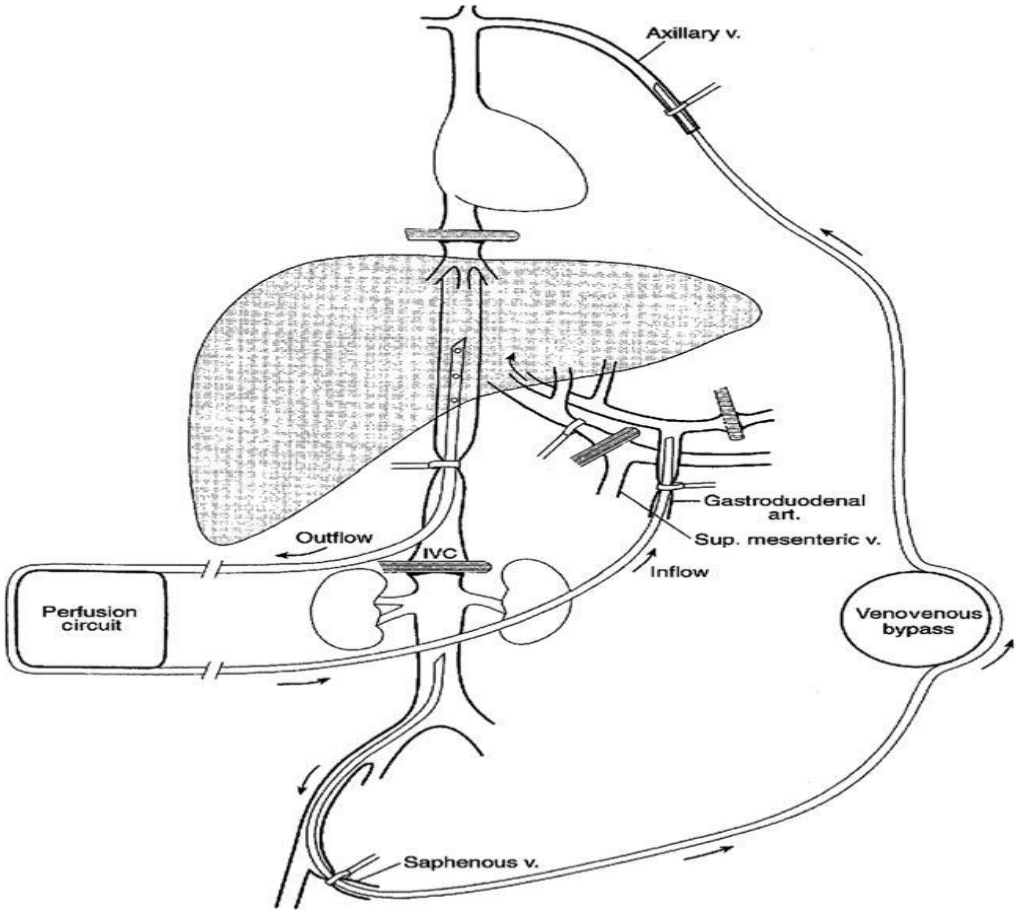

Fig (nº1): Illustration showing the isolated hepatic perfusion circuit. (Reddy SK et al. 2014) [2]

7.2 Ocular melanoma metastases

Uveal melanoma is the most common primary intraocular malignancy in adults, rare malignancy that arises from the uveal tract of the eye. Ocular melanoma is approximately 3 to 6% of all melanoma cases and 30 to 60% of this patient will develop some kind of metastases, liver metastases being the most typical place for metastases. Upon appearance of liver metastases, the survival period for this patient is highly lower, being less than 1 year of life, and death is usually due to the metastases advance in the liver making it not functional. When there is liver metastases subjacent to uveal melanoma systemic chemotherapy is not effective so this kind of treatment is exclude from possible treatment method, and there are no evidence-based guidelines for management of uveal melanoma liver metastases. Therefore, the treatment of choice might be aggressive regional therapy to control the progression of the disease in the liver. Several protocols and studies have been conducted to evaluate if IHP in patients with ocular melanoma liver metastases is better than systemic chemotherapy. [4], [7], [10], [11], [19]

7.3 Cutaneous Melanoma Metastases

Cutaneous melanoma is a disease cause by malignancy of pigment producing cells, melanocytes, mostly in the skin but also found in eyes, ears, gastrointestinal tract, oral and genital mucosa. In the skin it counts as less than 5 % of all skin cancers but is the type of skin cancer that causes the most deaths yearly. [16]

Melanomas give rise to complicated liver metastases which usually are unresectable and are a big challenge to the physician. Even though there have been a lot of advances in the systemic treatment for patients suffering with metastatic cutaneous melanoma to the liver, the overall prognosis is still quite poor, but it is still not as bad as when the metastases occur from ocular melanoma. Isolated hepatic perfusion, which allows high doses of cytotoxic chemotherapy to be directly delivered to the liver alone, minimizing the toxicity exposure to the system. So, this technique has emerged as a new possible treatment option for complex patients. [8]

7.4 Neuroendocrine Liver Metastases

A neuroendocrine tumor (NET) arises from specialized cells from the neuroendocrine system. These cells are both nerve cells and hormone-producing endocrine cells. They are throughout the whole body and organs and help to control body functions. As hormones are chemical substances that in the body are carried through the bloodstream to perform the specific effect they have in each cell or organ of the body. As they are carried in the bloodstream, the spread of these cancerous cells is very easy. [18]

Approximately 75% of patients suffering neuro endocrine cancer will have metastatic disease, and the most common site of metastases is the liver. As previously mention, the best treatment option is the partial resection of the part of the liver which is involve, as this can improve the 5-year survival rate more than 50% in cases where the surgery and achieved a complete resection of the tumor, but it is difficult to perform it as most of the patients usually present with bilateral or multifocal diseases which makes harder the resection or would leave not enough liver to be functional. Although when the liver metastases are diffuse and there is no surgical resection possibility there is a 5-year survival rate of approximately 30%

However, when there is no treatment, patients may develop other symptoms related to the tumor as debilitating local and systemic symptoms related to the tumor burden and hormone production. Also, liver directed therapies are proved to have a potential benefit to improve long term outcome by controlling the progression of the disease more accurately. Therefore, treatments of hepatic metastases have become of special importance in the management of patient with liver metastases.

7.5 Colo Rectal Liver Metastases

Colo Rectal cancer is a disease that arise from rectum or colon they are different disease but are most often group together as they have many common features. It usually starts as polyps growing in the inner lining but most of these polyps do not change into cancer and the ones who does it, it usually happens after some years. As cancer cells grow in the wall, they can also grow to the blood vessels and then spread into the blood flow, which leads to the spreading of the cancer. [9], [13], [14]

Because of the relatively high frequency of colorectal cancer liver metastases, most studies that have evaluated IHP as a treatment for liver metastases have been performed in patients with CRCLM as the data available is much higher than in other types of liver metastases. These studies have utilized multiple types of chemotherapy, including mitomycin C, oxaliplatin, and melphalan with and without TNFα, to see if there is significant variability between different types of treatment. [9], [12].

8. METHODOLOGY:

8.1 Literature Search and Selection of Records:

This review was conducted considering the 2020 PRISMA guidelines for systematic reviews with respect to different nominations of IHP in the past and without limiting the publication date, we systematically searched PubMed, Embase, ScienceDirect and the Google Scholar until 15 April of 2022 using the terms “isolated, liver, perfusion, chemotherapy and liver metastases” as MeSH Terms, as these terms represent the widest definition of isolated hepatic chemoperfusion and include the following translation:

Chemotherapy: “chemotherapy”, “drug therapy”, “chemotherapies”, “isolated perfusion”

Liver metastases: “uveal melanoma”, “cutaneous melanoma”, “ocular melanoma”, “neuroendocrine cancer”, “colorectal cancer”

Search period was limited to 15 years. After exclusion of other species than human and other languages than English, 3829 publications were eligible for the title, abstract, and full-text screening, which was performed independently by S.P.S without use of an automation tool.

I limited the analysis to studies that performed IHP directly on unresectable liver tumors. For this reason, there were not include any studies in which the main objective was the use of HIPEC instead of IHP as well as there were not any studies based on any kind of intraperitoneal chemotherapy.

Articles that present results with patient suffering for multiple tumor entities were also exclude as the result of the IHP was not well interpretated and the outcome of the disease could advance even if the hepatic metastases was well controlled.

In case of the multiple publications for the same origin of the prime tumor, the newest publication was selected.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Articles published in English language	Articles published in other languages
Articles published in the last 15 years. Being the range years from 2007 to 2022	Articles older than 15 years
Full text articles	Abstracts are not included in the study
Studies performed in humans	Studies not performed in humans
Priority of the publications: metanalysis review, randomized controlled trials, prospective studies, and retrospective studies	

8.2 Quality assessment.

As the main goal for this research was to determine the difference when an unresectable liver metastasis is treated with IHP technique, I have collected data with some patient studies in it

The main goal of this research was to provide and exhaustive overview of the differents outcomes for the treatment when the liver metastases come from different types of primary tumors throughout the body, as melanoma, uveal ad cutaneous, colorectal, and neuroendocrine tumors. therefore, each publication was assessed for the homogeneity of the of the patient with regard of the tumor precedence, as well as completeness report of IHP parameters as I deemed these parameters crucial for more accurate overview of this technique.

8.3 Data extraction

As I extracted all the data and search for the study, when there was some discrepancy when finding problems, Ž. Dambrauskas helped me to see if the data was adequate for the work or not. I systematically extracted data about IHP treatment for different kinds of metastases. If only the abstract was available, the data was not taken into consideration.

Articles selection:

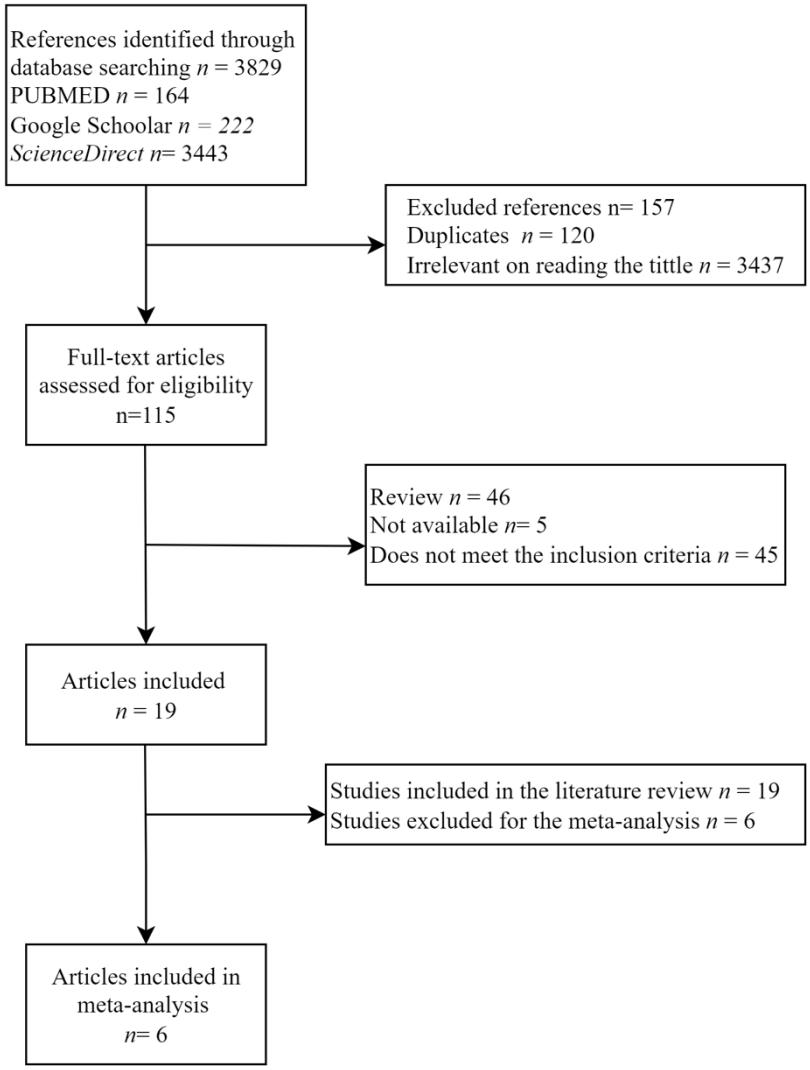

Fig 1: PRISMA Flow diagram for the review.

9. RESULT

9.1 Indication and outcomes of IHP in treatment of ocular melanoma metastases

There have been several studies researching what is the best possible treatment for liver metastases when the primary tumor is from ocular melanoma precedence. From thus studies it has been selected the most recent ones excluding repeated ones and not valid

A follow-up study reported outcomes in 29 patients with metastatic ocular melanoma to the liver treated at the NCI using IHP with melphalan alone. In this study, the overall response rate was 62% with three CRs (10%) and 15 PRs (52%). The actuarial median hepatic PFS within the 18 patients who demonstrated evidence of a response was 12 months and therefore the OS altogether patients were 12.1 months. There were no treatment-related deaths, and the most common side effect was transient grade III or greater hepatic toxicity, which occurred in 65% of patients. On statistical method, only baseline lactate dehydrogenase (LDH) was identified as a big independent prognostic factor for survival, suggesting that baseline LDH level may have a task in patient selection. [2]

Table 1.: result study IHP with melphalan treatment for ocular melanoma liver metastases.

Treatment IHP with melphalam	**OR**	**CR**	**PR**	**MEDIAN PFS**	**OS**
29	18 62%	3 10%	15 52%	12	12.1

OR, Overall Response; CR, Complete Response; PR, Partial Response; OS, Overall Survival

On other study done in Sweden, where just 11 patients where in the study, it was shown that in the first therapy, 6 patients median pfs of 10.4 months. [15]

Table 2.: results study 3 cycles with IHP for ocular melanoma liver metastases.

	CR	PR	SD	POST DEATH	SURVIVAL
IHP-I	0	6	2	3	7
IHP-II	2	6	0	3	13

IHP-III	0	5	0	0	5

[15]

CR, Complete Response; PR, Partial Response; SD, Stable Disease

9.2 Indication and outcomes of IHP in treatment of neuroendocrine liver metastases

The largest report in the literature which documents the use of IHP to treat neuroendocrine hepatic metastases is a study from the NCI. This report details treatment and outcomes in 13 patients with neuroendocrine liver metastases treated with IHP. Ten patients were treated with melphalan alone, two patients received a combination of melphalan and TNFα, and one patient was treated with TNFα alone. Reversible grade III/IV hepatic toxicity was observed in 62% of patients, which is consistent with toxicity observed in other IHP studies. There was one treatment-related mortality. Overall response was 50% and the median actuarial OS was 48 months. [2]

9.3 Indication and outcomes of IHP in treatment of colorectal cancer liver metastases

As CRCLM is the most common metastases in the liver this is the most studied type of liver metastases and where more data is found. As a result of the data studied during this work, there were a consideration in which the IHP treatment might be the best possible treatment in these patients, this statement is based on the data collected from several different studies.

9.3.1. Combinations of chemotherapy in colorectal cancer liver metastasis

A study done by the NCI (2) these results were note:

120 patients of which 69 were treated with melphalan, 41 with melphalan + TNFa 80% treated with chemotherapy before IHP. There were 5 treatment related deaths, 3 of them patients treated on phase I dose-seeking study

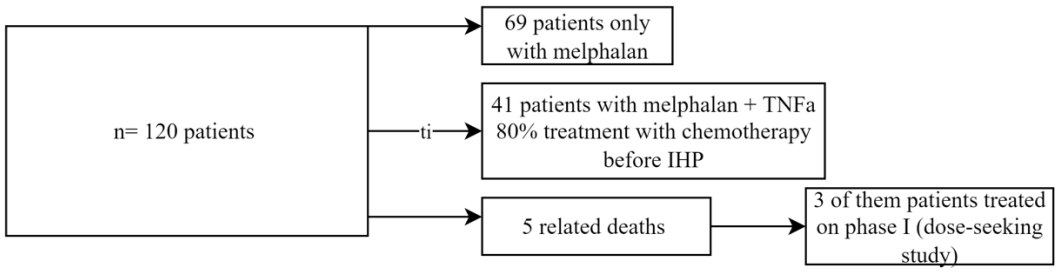

Fig. 2: Combinations of chemotherapy in CRCLM (Lawler M et al. 2020) (14)

Table n. 3.: Results different combinations of chemotherapy in CRCLM (14)

Treatment regimen	Number of evaluable patients	CR	PR	Median PFS months
Overall	114	2	67 59%	7.0
IHP–no HAI	58	0	33 57%	5.8
IHP–HAI	46	2	30 65%	13.0
IHP (TNF alone)	10	0	4	3.0

IHP, isolated hepatic perfusion; PR, partial response; CR, complete response; TNF, tumor necrosis factor; HAI, hepatic artery infusion.

The most common toxicities were transient elevations in serum transaminases and total bilirubin. Factors associated with response were higher doses of melphalan and the use of TNF. With respect to overall survival, only the use of HAI therapy and a preoperative carcinoembryonic antigen level of up to 30 ng/ml were significant on multivariate analysis.

Similar outcomes were reported by van Iersel [9] and colleagues who treated 105 patients with unresectable CRCLM over a 10-year period.,

105 patients ON 10 YEAR PERIOD, 200mg melphalan, Median progression-free survival 7.4 months, Median hepatic response 24.8-month, Overall response 50% (52/105), Adjuvant chemotherapy increase response and PFS.

More metastases, PV perfusion alone and postoperative complications decreased overall survival.

9.3.2. Only Melphalan chemotherapy treatment

Table 4.: results treatment only with melphalan in CRCLM

Treatment	Number	OR	CR	PR	MEDIAN PFS
200MG MELPHALAN	105	52 50%			7.4

[5], [9]

OR: Oral response CR: Complete Response PR: Partial Response

Using this same group of patients treated with IHP, van Iersel [9] and colleagues recently reported a case–control study that compared the use of IHP with melphalan to systemic chemotherapy in patients with unresectable CRCLM. The IHP group consisted of 99 patients. Showed that IHP was much better in younger patients.

In systemic chemotherapy 52% of patients had grade III/IV toxicity, 2%treatment related mortality, Overall response for IHP 47%, Progression diseases was 7.3 months, First line treatment 37% and disease progression 7.9, Not big difference in overall survival. 25 months for IHP and 21.7 for systemic chemotherapy., 50 patients with IHP as first line, overall survival of 28.9 and systemic was 24 months so not big differences.

10. DISCUSSION OF RESULTS

For uveal melanoma metastases, based on these studies, response rates of greater than 50% can be obtained using IHP with melphalan for unresectable ocular melanoma liver metastases. These results are better than those obtained with systemic therapy alone.

For neuroendocrine lever metastases, given the effectiveness of surgical resection and other liver-directed therapies in the management of patients with neuroendocrine liver metastases, it is likely that IHP will only play a significant role in the management of patients with quite advanced disease. Also, there were not many studies on this type of metastases.

With all these data put together, we can make few important questions regarding the treatment of colo-rectal cancer liver metastases. The role of new techniques as IHP for patients who have disease progression under the treatment of systemic chemotherapy and that do not have the possibility to undergo surgery for liver tumor resection, might be important in giving the patients more lifetime with better quality. But must be present that IHP performed alone is not better than systemic chemotherapy alone, but it is when they are given combined, with IHP as a second line treatment, after the systemic treatment has been given, might be the best treatment option.

So based on the result of different metastases from different primary cancers, IHP is beneficial for the patients when used after systemic chemotherapy has been given and the patient have improved so then, IHP have been proved to be beneficial.

Although tumor resection is still the gold standard treatment when it is possible.

10.1 Study limitations

The studies done for cutaneous melanoma liver metastases were older than the time needed for the review so there is not studies data for this type of disease.
During the review process, the main limitations I had faced were that most of the studies done review the isolated hepatic perfusion were carried out more than 15 years ago, so a lot of clinical trials had to be excluded from the review material

11. CONCLUSSION

1. Treatment of liver metastases from uveal melanoma is better with IHP than with systemic chemotherapy therefore in the patient with this kind of metastases when it is not possible to perform surgical total resection of the tumor, the best choice of treatment would be to perform.

2. Treatment for patient with liver metastases from neuroendocrine usually the surgical resection is enough because the metastases are not very aggressive.

3. When there are colo-rectal cancer liver metastases the best method to treat it is to give the patient firstly systemic chemotherapy and then as a second line treatment perform IHP so that there has been significant improvement in the patients' condition and life expectancy.

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13.ANNEX

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS

BIOETIKOS CENTRAS

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2022.04.14 Nr. BEC-MF-410

DĖL PRITARIMO TYRIMUI

LSMU Bioetikos centras, įvertinęs Sergio Pozueta Sangrones pateiktus dokumentus, studento tiriamajam darbui tema „Indications, technical considerations and rezults of isolated liver hyperthermic chemoperfusions: a systematic literature review“ pritaria*.

dr. Elmantas Peičius

* Pastaba: šis pritarimas neatleidžia tiriamąjį mokslinį darbą vykdančių asmenų nuo prievolės laikytis Bendrojo duomenų apsaugos reglamento nuostatų ir nuo atsakomybės gauti nacionalinio arba regioninio bioetikos komiteto leidimą, jei toks leidimas būtinas pagal LR Biomedicininių tyrimų etikos įstatyme numatytus reikalavimus.