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HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

Please contact: htamalaysia@moh.gov.my if you would like further information.

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AUTHORS:

DR. ANA FIZALINDA ABDULLAH SANI
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

MDM. ATIKAH SHAHARUDIN
Senior Principle Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

INFORMATION SPECIALIST:

MADAM ZAMILAH MAT JUSOH @ YUSOF
Nursing Officer / Information Specialist
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXPERT COMMITTEE

MISS NOR FARIZAN AZMI
Consultant General Surgeon (Colorectal)
Department of Surgery
Hospital Tuanku Ja'afar, Seremban

DR. YONG CHEE MENG
Consultant Obstetrics & Gynaecology (Gynae-Oncology)
Hospital Ampang

DR. NOOR ZAFIFAH ZAKARIA
Consultant Clinical Oncology
Hospital Kuala Lumpur

PROF.DR. ANDEE
Senior Lecturer and Consultant General Surgeon (Colorectal)
Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian

DR. ZOOL HILMI AWANG
Senior Consultant Specialist
Nuclear Medicine

DR. IZZUNA MUDLA MOHAMED GHAZALI
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS

DR. ROS SUZANNA AHMAD BUSTAMAN
Head of Department & Senior Consultant Clinical Oncology
Department of Radiotherapy & Oncology
Hospital Kuala Lumpur

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DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Background

Peritoneal surface malignancy (PSM) is a cancer arising from or spreading to the peritoneal surfaces and its represent an advanced form of abdominal malignancies with a grim prognosis and quality of life. It can be primary disease arising from the peritoneum or a secondary disease. Primary PSM is rare whilst secondary PSM is by far the most frequent. Primary PSM such as malignant peritoneal mesothelioma (MPeM) is a rare aggressive tumour of the peritoneum and have a poor prognosis. Secondary PSM is often cancers of the gastrointestinal tract, but it can be frequently arising from ovarian cancer and breast cancer.

Annual incidence of MPeM has been reported to be 0.2 to 0.3 cases per 1,000 000 people per year, globally. In United State of America, MPeM reported of 200 - 400 new cases diagnosed annually and, its incidence is increasing and expected to reach a peak in 2020 in Europe. Canada reported approximately 300 cases per year meanwhile in Finland, the incidence of MPeM was 0.74 cases per 1,000 000 people per year and the median survival time after diagnosis was four months. According to the French multi-institutional prospective study - Evoluation of Peritoneal Carcinomatosis or EVOCAPE 1 in 2000, the median survival in patients with MPeM was 5.2 months for those with advanced colorectal cancer, 3.1 months for those with advanced gastric cancer and, only 2.1 months for patients with pancreas cancer. Specifically, mesotheliomas are the cancers with the lowest five-year survival estimates at only 6.6% according to Office for National Statistics, Cancer Survival in England (2018).

The most common site of origin of this aggressive tumour arising from serous surfaces is pleura (65%-70%), peritoneum (30%), tunica vaginalis testis and pericardium (1%-2%). Mesotheliomas have a three basic histologic forms; epithelioid (the most frequent), sarcomatoid or mixed biphasic. The most frequently initial symptoms are abdominal pain (35%), abdominal swelling (31%), anorexia, marked weight loss, and ascites.

Formerly, these types of malignancies were considered incurable conditions and have been regarded as a terminal condition for palliative care. A well-known mentor, Dr. Paul Sugarbaker showed that surgical removal of visible tumour for MPeM combined with locoregional heated chemotherapeutic drugs improved the survival and quality of life of these patients. Subsequencely, the treatment paradigm of PSM has thus evolved from one of palliation to one of using multimodality therapy in an attempt to bring about long-term survival to patients with an acceptable rate of morbidity.

Cytoreductive surgery (CRS) encompasses a wide range of accepted complex oncologic procedures namely hepatectomy, pancreaticoduidenectomy (Whipple), esophagectomy, and from resection of one peritoneal nodule to multivisceral resection with peritoneal stripping. Therefore, these procedures reflect a wide range of possible morbidity.

Cytoreductive surgery and hyper thermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal malignancies is practice at many centres and have been used as a standard but the literature is scarce in many aspects related to the management of CRS-HIPEC. CRS-HIPEC is a standard combined treatment modality treatment for resectable tumours at diagnosis, is an aggressive locoregional treatment that has been available as a treatment option for peritoneal carcinomatosis since the mid-1990s. The surgical procedure involves debulking and stripping of the diseased peritoneum and multiple visceral organ resections. Following the surgery, a heated chemotherapy is administered intraoperatively into the abdomen to cover all raw peritoneal surfaces. In 1990s, cytoreduction combined with intraperitoneal chemotherapy was considered for patients with peritoneal mesothelioma. In addition, hyperthermia has been demonstrated to have a synergic effect with the chemotherapy and can thus enhanced the cytotoxicity of the drug.

Technical Description of Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Two different techniques for the delivery of HIPEC:

i. In closed techniques, inflow and outflow perfusion catheters are placed into the abdomen (intra-abdominally) and the skin edges are closed while
ii. in open techniques the skin edges are not approximated. Instead, the skin is secured to the abdominal retractors and plastic drapes and are sewn to the skin edges to act as a partial barrier to contain the chemotherapy solution and prevent heat loss.

Each technique has its advantages and disadvantages. In closed techniques, the surgeons may more easily maintain consistent intra-abdominal temperature. This technique offers less chance for chemotherapy spillage, and reduces the potential for toxic vapour escape into the room atmosphere. In open technique, the surgeons may better assure all the surfaces of the intra-abdominal organs are bathed by the chemotherapy solution, but the chances of spillage are greater and no assurances that chemotherapy vapours are properly evacuated. More surgeons used a closed system with an FDA-authorised or commercially available perfusion machine for HIPEC. The role for direct drug delivery to the peritoneal and tumour surfaces was described and reported in multiple review of cisplatin administration where the chemotherapeutic agents were delivered intraperitoneal at concentrations up to 30 times greater than those safely administered via intravenous route.

Role of Hyperthermia

Hyperthermia alone is cytotoxic at the cell and tissue levels with formation of heat shock proteins. HIPEC combined the pharmacokinetic advantage inherent to the intra cavity delivery of certain cytotoxic drugs which results in regional dose of intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself and enhances the tissue penetration of the administered drug. HIPEC required the spread of cytostatic drugs during the surgical intervention at high temperature (41 – 43°C) within 60 to 120 minutes.

Perioperative management of CRS-HIPEC consist of:

- eligibility for the CRS-HIPEC procedure
- perioperative staging and assessment

In Malaysia, access to this treatment option is limited as it only available at University Malaya Medical Centre and few of private hospitals. Hence, this timely health technology assessment (HTA) was requested by the former General Surgeon and Colorectal Specialist, Ministry of Health Malaysia to assess the efficacy, safety and cost-effectiveness of HIPEC to be introduced within Ministry of Health (MOH) facilities in treating patient with PSM.

Policy Question

Should hyperthermic intraperitoneal chemotherapy (HIPEC) be introduced and initiated as an adjuvant therapy with cytoreductive surgery (CRS) in Ministry of Health facilities?

Objectives

i. To assess the effectiveness and safety of CRS-HIPEC in patients colorectal carcinomatosis peritoneal metastases (CRC PM) and other gynae-oncological diseases compared with standard medical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone with regards to patient outcomes such as overall survival, progression-free survival, perioperative and postoperative mortality, health-related quality of life, quality adjusted life years (QALY) gained, and adverse events/complications.

ii. To assess the economic impacts of using HIPEC treatment in patients colorectal carcinomatosis peritoneal metastases (CRC PM) and other gynae-oncological diseases compared with standard surgical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone.

iii. To assess the ethical, social, and organisational aspects related to HIPEC treatment.

Research Questions

i. How effective is HIPEC as adjuvant therapy with CRS compared with standard surgical procedures / treatment,
ii. Is HIPEC safe when used for adjuvant therapy?
iii. What is the economic, ethical, social, and organisational implication/impact related to adjuvant therapy CRS with HIPEC?

Methods

Literature search was conducted by an *Information Specialist* who searched for published articles pertaining CRS and HIPEC treatment in patients colorectal carcinomatosis peritoneal metastases (CRC PM) and other gynae-oncological diseases. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2021, EBM Reviews - Health Technology Assessment (4th Quarter 2020), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2021), EBM Reviews - Cochrane Central Register of Controlled Trials (December 2020), and EBM Reviews - NHS Economic Evaluation Database (1st Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Detailed search strategy is as in **Appendix 3**. The last search was performed on 31 December 2020. Additional articles were identified from reviewing the references of retrieved articles.

Results:

A total of 1760 records were identified through the Ovid interface and PubMed while 25 were identified from references of retrieved articles. After removal of 71 duplicates, 730 titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, 35 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 35 full text articles, 15 full text articles were included. The **15 full text articles finally selected for this review comprised of seven systematic review and meta-analysis, one systematic review on randomised controlled trials (RCTs), five systematic review of non-RCTs, and two economic evaluation studies.** The studies were conducted mainly in European countries, United States of America, China and Korea. The two economic evaluation studies were from Singapore and Australia.

A. EFFECTIVENESS

a. Colorectal cancer

Generally, two systematic review of non-RCTs showed that pooled median overall survival (OS) across of all studies for patients received CRS and HIPEC was 32 months (range 12.2 – 60.1 months) when comparing with no HIPEC group as a control. However, in another systematic review, stated that the 3- or 5- year OS showed that patients undergoing HIPEC treatment demonstrated no survival time benefit compared to those undergoing standard treatment without HIPEC (RR: 1.13; 95% CI: 0.97 to 1.33; p= 0.12; I^2=77%). Similarly, 3- or 5-year progression-free survival (PFS), disease free survival (DFS) also did not showed the expected efficacy of preventive HIPEC treatment in improving the survival for patients in CRC with high risk of peritoneal carcinomatosis (PC). (RR= 1.10; 95% CI: 0.75 to 1.59; p = 0.63; I^2 = 53%); (RR= 0.41; 95% CI: 0.21 to 0.83; p = 0.01; I^2 = 58%).

In addition to completeness of cytoreduction (CC), increasing peritoneal carcinomatosis index (PCI) and lymph node involvement, factor related to primary tumour location, adjuvant chemotherapy and perioperative grade III/IV morbidity are also key prognostic factors influencing survival in patients

undergoing CRS + HIPEC for isolated CRPM. While CRS and HIPEC as a combined treatment has been demonstrated to be superior to systemic chemotherapy in CRPM, there a very few studies have evaluated the role of CRS alone without HIPEC.

Colonic origin of PM showed better outcomes and prognosis (OS and PFS) when compared with rectal origin PM.

b. Gynae related

Endometrial Cancer-derived Peritoneal Metastase (EC-derived PM):

CRS and HIPEC treatment for patients with EC-derived PM demonstrated a median OS of 12 to 33 months and a median DFS was 7 to 18 months.

CRS and HIPEC are effective when the patient achieved a CC=0 resection in 70% of the patients with endometrial cancer-derived PM.

c. Ovarian Cancer:

HIPEC as an adjuvant may improve DFS of patients with ovarian cancer when residual tumours were ≤1 cm or not visible. (DFS: HR= 0.580; 95% CI 0.476 to 0.706) HIPEC treatment also improved the prognosis in both primary and recurrent disease. However, the effect of HIPEC was not observed in patients with primary disease who had residual tumours ≤1 cm or no visible tumours. It may also improve OS of only patients with recurrent disease whose residual tumours were ≤1 cm. (OS: HR= 0.611; 95% CI, 0.376 to 0.99)

For women with recurrence ovarian cancer (ROC) and be treated with CRS+HIPEC and chemotherapy, OS showed a significantly improved 1-year OS when compared to protocols without HIPEC (OR= 2.42; 95% CI, 1.06 to 5.56; p=0.04; I^2 =4%) and maintained significant improvement in OS after 2-, 3- and 5- years respectively. (2-years OS= OR: 3.33; 95% CI, 1.81 to 6.10; p<0.01; I^2=0%); 3-years OS: (OR= 4.22; 95% CI, 2.07 to 8.60; p<0.01; I^2 =52%); 5-years OS: (OR= 5.17; 95% CI, 1.40 to 19.09; p=0.01; I^2 =82%)

Safety

Generally, CRS + HIPEC in combination with systemic modern chemotherapy regimens was introduced by using different chemotherapy agents with different toxicity. The most common adverse effects (AEs) such as nausea were similar to post chemotherapy procedure. Adverse events (AEs) grade 1 and 2 were mostly observed in those patients compared to grade 3 and 4. Meanwhile, a treatment-associated mortality was reported as 1%. Most of AEs reported could be resolved by standard care treatment such as anti-emetics.

Oxaliplatin showed a higher proportion of severe complications compared to mitomycin C (MMC) based as chemotherapeutic agents for HIPEC in patients with CRC-PM.

Organisational

Total procedure or operation time (median) varied widely based on surgeon techniques and experiences, ranging from 149.3 minutes (range 79-185 minutes) and hospital stay was 4.6 days (range 2-11 days) respectively.

The chemotherapy solution is prepared in the pharmacy department and it is sent to the operating room in a closed light-protected bag with appropriate labelling which is handled with double gloves and the integrity of the bag is checked. Any leak detected results in the bag being returned to the pharmacy department. If the bag is approved there is no risk of direct exposure and it is given to the person responsible for the perfusion, who must check the patient's name, drug and dose delivered against those prescribed.

Training of the for the specialised team is needed to conduct this treatment along with a proper radiation centre for handling the toxic waste and measurement secured.

A designated operating room is needed for the smooth operating procedure when HIPEC treatment is introduced to a centre.

Economic implication

Overall, CRS and HIPEC treatment results in significant increases in medical costs with a parallel increase in survival for a disease that has been poorly treated, and hence may be considered as cost-effective given the observed life years gained. There were two studies on cost-analysis retrieved.

The first economic evaluations examined the cost effectiveness of CRS+ HIPEC compared with palliative chemotherapy for patients with peritoneal carcinomatosis from colorectal cancer (CRC PM) within the context of the Singaporean health care system. The average cost for CRS+HIPEC appears to be higher than for palliative chemotherapy (S$83,680.26 vs S$44,478.87). However, prolonged survival and lower readmission rates are enjoyed by this group of patients compared with a matched group of patients treated with palliative chemotherapy. With a difference in median survival of 38 months, at a cost difference of S$37,939.97, the cost per life year attained in the CRS+HIPEC group was significantly lower than the cost per life year attained in the palliative chemotherapy group.

In another economic evaluation studies, measure and describe the survival outcomes and healthcare cost associated with CRS and HIPEC for peritoneal surface malignancies (PSM) at a centralised tertiary institution in Australia. The average cost of CRS and HIPEC per patient and per life year for appendix cancer is AUD $88,423 (range: AUD $23,933–AUD $299,145) and AUD $37,737/LY. Colorectal cancer is AUD $66,148 (range: AUD $26,079–AUD $409,666) and AUD $29,757/LY; for pseudomyxoma peri tonei is AUD $92,308 (range: AUD $11,562–AUD $501,144) and AUD $29,559/LY; for peritoneal mesothelioma is AUD $55,062 (range: AUD $23,261–AUD $94,104) and AUD $20,521/LY; and for other peritoneal surface malignancies is AUD $44,668 (range: AUD $31,592–AUD $70,026) and AUD $22,091/LY.

Conclusion

The availability of evidence differs between targeted group of patients, origin of the disease, technique and chemotherapy agents use in the procedure. There was fair to good level of retrievable evidence to suggest CRS and HIPEC treatment comparing to standard procedure and treatment, CRS alone and systemic chemotherapy alone. Generally, it is a safe and may benefit patients according to the selection criteria of the patient's profile; such as the type of cancer origin, perioperative selection (completeness of cytoreduction (CC), increasing peritoneal carcinomatosis index (PCI) and lymph node involvement) and the chemotherapeutic agents involved.

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HEALTH TECHNOLOGY ASSESSMENT (HTA)

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) AS AN ADJUVANT THERAPY FOR PERITONEAL SURFACE MALIGNANCY (PSM)

1.0 BACKGROUND

Progress in the management of peritoneal metastases from gastrointestinal and gynecologic malignancy has continued over the last three decades. Cytoreductive surgery (CRS) with peritonectomy procedures and visceral resections have become well defined and are currently completed with minimal morbidity and mortality. The second component of peritoneal metastases treatment is hyperthermic perioperative chemotherapy (HIPEC). This has progressed but to this point in time standards of care have not been formulated.

Peritoneal surface malignancy (PSM) is a cancer arising from or spreading to the peritoneal surfaces and its represent an advanced form of abdominal malignancies with a grim prognosis and quality of life. [1,2,3,4] It can be primary disease arising from the peritoneum or a secondary disease. Primary PSM is rare whilst secondary PSM is by far the most frequent.[4,5] Primary PSM such as malignant peritoneal mesothelioma (MPeM) is a rare aggressive tumour of the peritoneum and have a poor prognosis.[6,7,8] Secondary PSM is often cancers of the gastrointestinal tract, but it can be frequently arising from ovarian cancer and breast cancer.[4]

Annual incidence of MPeM has been reported to be 0.2 to 0.3 cases per 1,000 000 people per year, globally. In United State of America, MPeM reported of 200-400 new cases diagnosed annually and, its incidence is increasing and expected to reach a peak in 2020 in Europe.[9] Canada reported approximately 300 cases per year[10,11] meanwhile in Finland, the incidence of MPeM was 0.74 cases per 1,000 000 people per year and the median survival time after diagnosis was four months.[12] According to the French multi-institutional prospective study - Evoluation of Peritoneal Carcinomatosis or EVOCAPE 1 in 2000, the median survival in patients with MPeM was 5.2 months for those with advanced colorectal cancer, 3.1 months for those with advanced gastric cancer and, only 2.1 months for patients with pancreas cancer.[9,13] Specifically, mesotheliomas are the cancers with the lowest five-year survival estimates at only 6.6% according to Office for National Statistics, Cancer Survival in England (2018).[14]

The most common site of origin of this aggressive tumour arising from serous surfaces is pleura (65%-70%), peritoneum (30%), tunica vaginalis testis and pericardium (1%-2%). Mesotheliomas have a three basic histologic forms; epithelioid (the most frequent), sarcomatoid or mixed biphasic. The most frequently initial symptoms are abdominal pain (35%), abdominal swelling (31%), anorexia, marked weight loss, and ascites.[6]

Formerly, these types of malignancies were considered incurable conditions and have been regarded as a terminal condition for palliative care.[1] A well-known mentor, Dr. Paul Sugarbaker showed that surgical removal of visible tumour for MPeM combined with locoregional heated chemotherapeutic drugs improved the survival and quality of life of these patients.[7,14,15] Subsequencely, the treatment paradigm of PSM has thus evolved from one of palliation to one of using multimodality therapy in an attempt to bring about long-term survival to patients with an acceptable rate of morbidity.[3]

Cytoreductive surgery (CRS) encompasses a wide range of accepted complex oncologic procedures namely hepatectomy, pancreaticoduidenectomy (Whipple), esophagectomy, and from resection of one peritoneal nodule to multivisceral resection with peritoneal stripping. Therefore, these procedures reflect a wide range of possible morbidity.[8]

Cytoreductive surgery and hyper thermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal malignancies is practice at many centres and have been used as a standard but the literature is scarce in many aspects related to the management of CRS-HIPEC.[7] CRS-HIPEC is a standard combined treatment modality treatment for resectable tumours at diagnosis, is an aggressive locoregional treatment that has been available as a treatment option for peritoneal carcinomatosis since the mid-1990s. [6,8, 16, 17] The surgical procedure involves debulking and stripping of the diseased peritoneum and multiple visceral organ resections. Following the surgery, a heated chemotherapy is administered intraoperatively into the abdomen to cover all raw peritoneal surfaces. In 1990s, cytoreduction combined with intraperitoneal chemotherapy was considered for patients with peritoneal mesothelioma. In addition, hyperthermia has been demonstrated to have a synergic effect with the chemotherapy and can thus enhanced the cytotoxicity of the drug.[18] **(See Figure 1)**

2.0 TECHNICAL FEATURES

Technical Description of Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Two different techniques for the delivery of HIPEC:

iii. In closed techniques, inflow and outflow perfusion catheters are placed into the abdomen (intra-abdominally) and the skin edges are closed while

iv. in open techniques the skin edges are not approximated. Instead, the skin is secured to the abdominal retractors and plastic drapes and are sewn to the skin edges to act as a partial barrier to contain the chemotherapy solution and prevent heat loss.

Each technique has its advantages and disadvantages. In closed techniques, the surgeons may more easily maintain consistent intra-

abdominal temperature. This technique offers less chance for chemotherapy spillage, and reduces the potential for toxic vapour escape into the room atmosphere. In open technique, the surgeons may better assure all the surfaces of the intra-abdominal organs are bathed by the chemotherapy solution, but the chances of spillage are greater and no assurances that chemotherapy vapours are properly evacuated.[3] More surgeons used a closed system with an FDA-authorised or commercially available perfusion machine for HIPEC.[19] The role for direct drug delivery to the peritoneal and tumour surfaces was described and reported in multiple review of cisplatin administration where the chemotherapeutic agents were delivered intraperitoneal at concentrations up to 30 times greater than those safely administered via intravenous route.[20]

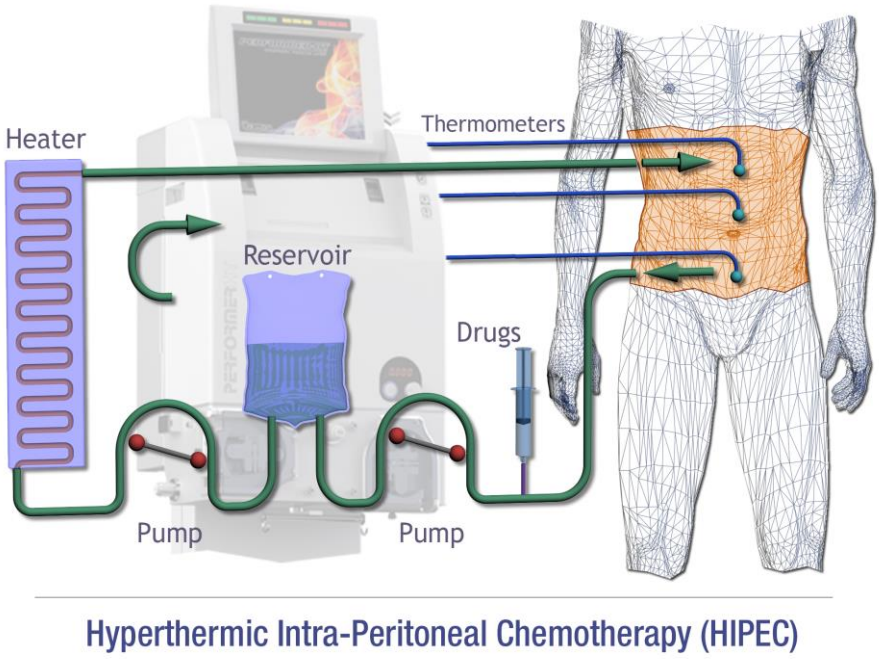

Figure 1: HIPEC: How it works

Role of Hyperthermia

Hyperthermia alone is cytotoxic at the cell and tissue levels with formation of heat shock proteins.[20, 21] HIPEC combined the pharmacokinetic advantage inherent to the intra cavity delivery of certain cytotoxic drugs which results in regional dose of intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself and enhances the tissue penetration of the administered drug.[22] HIPEC required the spread of cytostatic drugs during the surgical intervention at high temperature (41 – 43°C) within 60 to 120 minutes.[22, 23]

Perioperative management of CRS-HIPEC consist of:

- eligibility for the CRS-HIPEC procedure
- perioperative staging and assessment

In Malaysia, access to this treatment option is limited as it only available in our local health care facilities; at University Malaya Medical Centre and few of private hospitals. Hence, this health technology assessment (HTA) was requested by the former General Surgeon and Colorectal Specialist, Ministry of Health Malaysia to assess the efficacy, safety and cost-effectiveness of HIPEC on health outcomes in treating patient Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases.

3.0 POLICY QUESTION

Should hyperthermic intraperitoneal chemotherapy (HIPEC) as an adjuvant therapy with Cytoreductive Surgery (CRS) be initiated and structured in Ministry of Health facilities?

4.0 OBJECTIVES

4.1 To assess the effectiveness and safety of CRS-HIPEC in patients Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases compared with standard medical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone with regards to patient outcomes such as overall survival, progression-free survival, perioperative and postoperative mortality, health-related quality of life, quality adjusted life years (QALY) gained, and adverse events/complications.

4.2 To assess the economic impacts of using HIPEC treatment in patients with Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases compared with standard surgical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone.

4.3 To assess the ethical, social, and organisational aspects related to HIPEC treatment.

4.2 Research Questions

i. How effective is HIPEC as adjuvant therapy with CRS compared with standard surgical procedures / treatment,
ii. Is HIPEC safe when used for adjuvant therapy?
iii. What is the economic, ethical, social, and organisational implication/impact related to adjuvant therapy CRS with HIPEC?

5.0 METHODS

5.1. Search Strategy

Electronic database will be searched for published literatures pertaining to BLVR for emphysema treatment.

5.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database will be searched.
5.1.2 Additional literatures will be identified from the references of the retrieved articles.
5.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
5.1.4 There will be no limitation applied in the search such as year and language.
5.1.5 The search strategy will be included in the appendix.

5.2 Inclusion and Exclusion Criteria

5.2.1 Inclusion Criteria

a. Population :
- Pseudomyxoma Peritonei
- Malignant Mesothelioma
- Peritoneal metastases
- advanced gastric cancer
- gynaecologic cancer

- Advanced gastric ca/stage IV = Peritoneal carcinomatosis?

b. Intervention : CRS plus HIPEC

c. Comparators :
- CRS alone
- Systemic chemotherapy alone

d Outcome

i. Effectiveness of survival rates/ overall survival/5-years survival rate
ii. Safety
- adverse events
- minor/major complications

iii. Health-related quality of life
iv. Economic impacts
v. Cost-effectiveness
vi. Cost-utility
vii. Cost-benefit
viii. Organisational issues
ix. Hospital utilisation (readmission, length of stay, and emergency department presentations)
x. Training or learning curve to perform the procedure
xi. Ethical issue
xii. Social implication (e.g. patient satisfaction)

e. Study design : HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), and economic evaluation studies

f. English full text articles

5.2.2 Exclusion Criteria

a. Study design : Animal study, laboratory study, cohort, case-control, cross-sectional studies, narrative review
b. Non English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

5.3 Critical Appraisal of Literature

The risk of bias of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) and The Cochrane Collaboration's tool for RCT.

5.4 Analysis and Synthesis of Evidence

5.4.1 Data extraction strategy

The following data will be extracted:

i. Details of methods and study population characteristics
ii. Detail of intervention and comparators
iii. Details of individual outcomes specified

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

5.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness associated with HIPEC as adjuvant therapy with CRS for the treatment of Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5.5 Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the *Critical Appraisal Skills Programme (CASP)* [31] tool depending on the type of study design, and was conducted by two reviewers. *The Cochrane Collaboration's tool* for assessing risk of bias of RCT is an example of a component approach which is also use by MaHTAS. It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues). All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (**Appendix 1**).[32-33]

6.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 3.** A total of **1760** records were identified through the Ovid interface and PubMed while **25** were identified from references of retrieved articles. After removal of **71** duplicates, **730** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **35** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **35** full text articles, **15** full text articles were included. A total of **15** full text articles were excluded since the studies were already included in systematic review and meta-analysis (n=15), irrelevant study design (n=3) and irrelevant intervention (n=2). The excluded articles are listed in **Appendix 5**.

The **15** full text articles finally selected for this review comprised of **seven** systematic review and meta-analysis, **one** systematic review with RCTs, **five** systematic review of non-RCTs, and **two** economic evaluation studies.

The studies were conducted mainly in United States, European countries, China and Korea. The two economic studies were from Singapore and Australia.

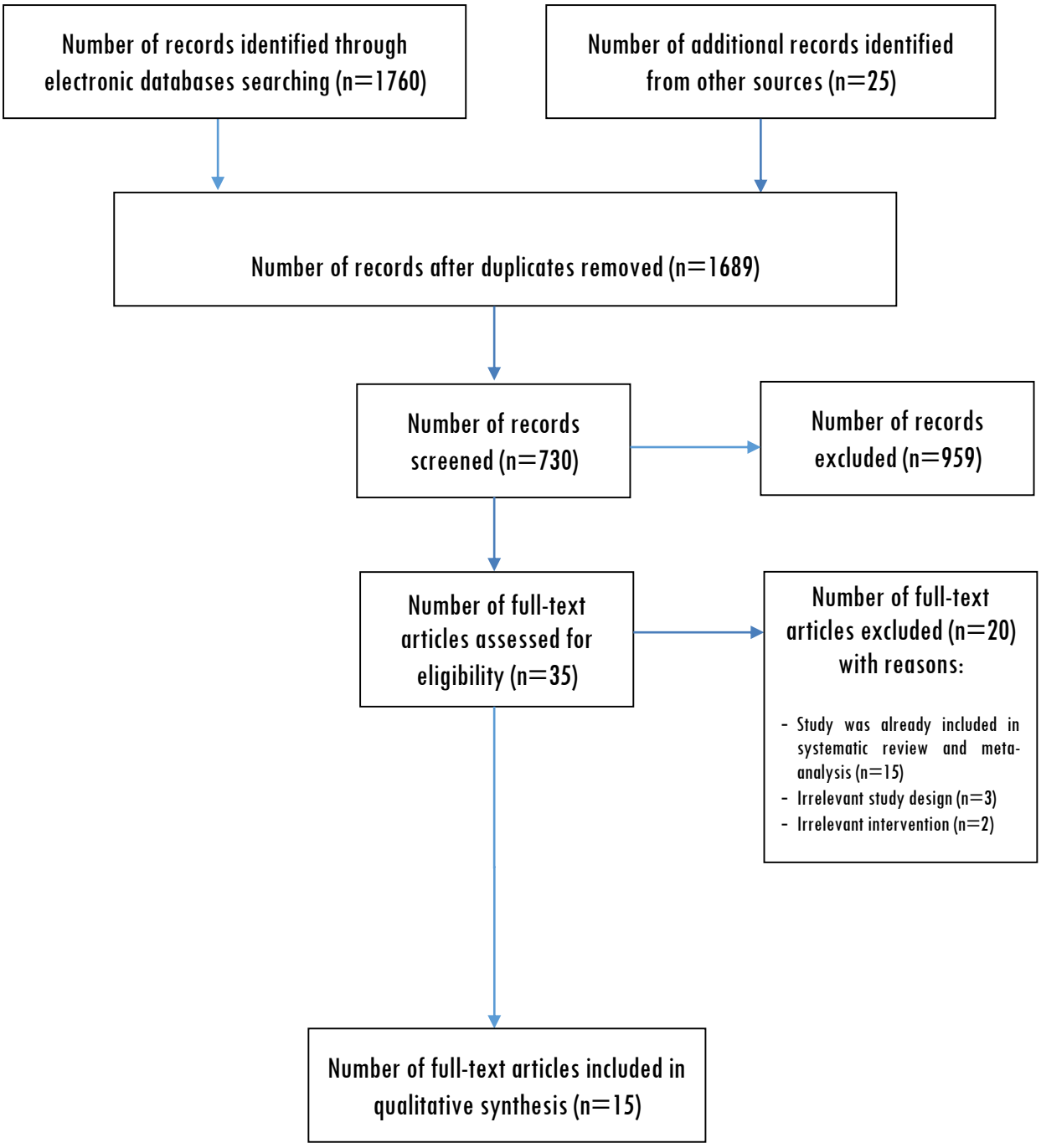

Figure 3: Flow chart of retrieval of articles used in the results

Risk of bias assessment:

The risk of bias in the included studies were assessed using domain-based evaluation. For RCT, Cochrane Collaboration Tool for assessing risk of bias comprising of six domains was used whereas for other studies, the tools that are being used by MaHTAS to assess the risk of bias are adapted from the CASP checklist. This is achieved by

answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates low risk of bias
?	indicates unclear risk of bias
-	Indicates high risk of bias

Overall, the risk of bias was low for SRs, RCTs, and economic evaluation studies. Although some of the RCTs and the pre- and post- interventional studies in this review were non-blinded due to the nature of the interventions under investigation, there were not leading to bias or classified as being at a high risk of performance bias. Besides, most of the studies were limited by the sample size or small case number. The results of risk of bias of included studies are summarised in **Figure 4.1 to 4.4**

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
ZHAO PY 2020	+	+	+	+
HALLAM S 2019	+	+	-	+
TONELLO 2019	+	-	+	+
FLOOD M 2020	+	-	+	+
NARAMSINHAM V 2020	+	+	-	+
WISSELINK DD 2019	+	-	+	+

Figure 4.1: Assessment of risk of bias of systematic review (CASP)

6.1 EFFECTIVENESS

6.1.1 Colorectal Cancer (CRC), Colorectal peritoneal metastases (CRPM)

Zhao ZY et al. in 2020 conducted a systemic review with meta-analysis with aim to evaluate the clinical efficacy and safety of HIPEC in colorectal cancer (CRC) patients with at high risk of peritoneal carcinomatosis (PC). In this SR, using a comprehensive literature search, irrespective of language, was conducted in multiple online databases including in PubMed, Embase, and Cochrane Library with last search up to July 30, 2020. Studies were also identified by screening the reference lists of systematic reviews on similar subjects. The current study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements and quality assessments and risk of bias were assessed using Newcastle-Ottawa Scale (NOS). Six (6) clinical studies met the criteria and were included in this meta-analysis which consist of four (4) observational studies and two RCTs); with a total number of selected participants of 603 patients.

Among the eligibility studies were selected using the inclusion criteria as follow:

- clinical studies comparing the efficacy and safety of HIPEC administration with control groups that did not undergo HIPEC treatment
- among adult CRC patients at high risk of PC (minimal PC that was completely resected at the same time as the primary tumour; synchronous or metachronous ovarian metastasis; perforated primary tumour inside the peritoneal cavity for some pathologies or iatrogenic reasons),
- regardless of study type (RCTs or non RCTs)
- Considering the limited evidence on gray data, we did not include conference abstract-type research

And the exclusion criteria are:

- studies with CRC patients who had developed peritoneal metastases or liver mets
- studies with no control groups or with CRC patients in the control group who also underwent HIPEC treatment
- studies involving PM that might have originated from areas other than a colorectal origin
- ongoing clinical trials
- studies with a with a lack of sufficient information or without follow-up.

Results:

Two studies administered HIPEC treatment only in the experimental group while the remaining 4 studies conducted treatment by HIPEC combined with curative surgery or adjuvant systemic chemotherapy in the intervention group. The majority of studies also chose OS as the primary outcome, while Goéré, Charlotte, and Elias selected 3-year DFS, 18-month PFS, and 3-year DFS, respectively, as their first outcome.

3- or 5-year overall survival (OS):
In a group of CRC patients at high risk of PC who were undergoing HIPEC treatment had no survival time benefit compared to those undergoing standard treatment without HIPEC (RR: 1.13; 95% CI: 0.97 to 1.33; *p* = 0.12; I^2 = 77%).

3- or 5-year disease-free survival (DFS):
There are three studies; with a total number of patient (n=238) and results showed that HIPEC treatment did not extend the DFS of CRC patients at high risk of PC (RR: 1.10; 95% CI: 0.75 to 1.59; *p* = 0.63; I^2 = 53%)

3- or 5-year progression free survival (PFS):
Two studies with a total number of (n=268) in the HIPEC group did not show the expected efficacy (RR: 1.85; 95% CI: 0.48 to 7.14; p = 0.37; I^2= 93%). In addition, due to high heterogeneity, through sensitivity analysis, found that Charlotte's study was the main source of heterogeneity and that if this review excluded this study, the robustness of the conclusion would also be affected (RR: 3.75; 95% CI: 1.88 to 7.47; p < 0.01)

The incidence of peritoneal metastasis (PM) after treatment was documented in all eligible studies. Also, the prophylactic HIPEC treatment significantly reduced the incidence of peritoneal metastases in CRC patients at high risk of PC compared to the control group (RR: 0.41; 95% CI: 0.21 to 0.83; *p* = 0.01; I^2 = 58%). Sensitivity analysis done and conclusion was quite stable.

A systematic review and meta-analysis by Hallam S et al. in 2019 which included 24 cohort studies described 3128 patients. This review aimed to identify the prognostic factors for patients with CRC PM undergoing CRS and HIPEC as their multimodality treatment. In this SR, six prospective studies and 18 retrospective studies were included using CRS and HIPEC as their intervention and pooled median follow-up was 28.1 months (range: 13.3 to 62.4 months). Most of the included studies reported on the impact of prognostic factors on the overall survival (OS) and pooled media OS across all studies was 32 months (range: 12.2 to 51 months).

Among prognosis factors listed in this review were patient factors, (age, sex, ECOG status) tumour factors, (rectal or colonic primary, lymph node metastasis, tumour differentiation, ascites, histology type, gastrointestinal anastomosis, peritoneal carcinomatosis index (PCI)) and lastly treatment factors (previous surgical score, postoperative morbidity, neoadjuvant chemotherapy, completeness of cytoreduction).

Tonello M et al. in 2019 conducted a SR with MA consist of nine studies with aim to analyse the survival of patients treated with CRS+HIPEC according to the origin of PM. A total number of participants in this review were (N=1153) which consist of all patients who majority were affected by colonic pm (88.2%) and rectal pm (11.8%).

In this study, the authors defined the term colon as intraperitoneal large bowel portion and rectum were defined as extraperitoneal.

The Inclusion criteria are as follow:

- patients with CRPM pathological confirmation, treated with CRS+HIPEC; every chemotherapy regimen, e.g. Oxaliplatin "bidirectional", Cisplatin & Mytomicin C, Mytomicin C alone, etc.) or CRS & EPIC or CRS and HIPEC followed by EPIC
- CC=0 or CC=1 scored
- reported complete survival data: OS and/or DFS/HR with CI
- data reported dividing primary tumour origin (colon vs rectum, considering rectum only the extraperitoneal section of bowel

The exclusion criteria are as follow:

- CC2 or CC3 regardless the association of HIPEC/EPIC
- review and duplicated articles
- editorials & non-English papers, radiologic or pharmacokinetics research, QOL assessment articles, commentary, letter, book, and others
- studies that did not separate results according to primary tumour site
- incomplete data on survival

Results:
The survival analysis was performed in two main sections OS & DFS; which calculated started from CRS+HIPEC. The OS survival were divided in two sub-groups because there were five articles reported mean OS (subgroup A), whereas another three articles reported only survival HR of rectal PM compared to colonic PM (subgroup B).

- Survival analysis demonstrates that colonic origin of PM relates with a longer OS and DFS, compared to rectal origin of PM
- mean difference OS= 24,49 months > for colonic PM [95% CI: 14,70 to 34,28 months; p < 0,000001 and
- pooled rectal PM HR= 1.62 [95% CI 1,01 to 2,59; p: 0,05] compared to colonic PM
- DFS > for colon PM; mean difference DFS= 7,75 months greater [95% CI: 1,37 to 14,13 months, p: 0,02]
- Heterogeneity is high among studies in OS subgroup A analysis (reported mean OS); I2=98%, p < 0,000001)

In addition, the DFS analysis (I^2= 91%; *p*< 0,000001 (group A) whereas in OS subgroup B (reported HR) analysis is low (I2= 25%, p: 0,26. The analysis of DFS could be performed only in four studies, because other included study does not report DFS ourcomes.

Flood FM et al. in 2020 conducted a SR of cohort studies with aim to evaluate the outcomes following the procedure of CRS+HIPEC for colorectal peritoneal metastases (CRPM) from published high volume cohort studies and keen to highlight the latest controversies and future directions of CRPM treatment. In

this review, 20 retrospective cohort with a number of patients (n=5552) were included.
The inclusion criteria were as follow:

- English studies
- with over 100 patients, reporting on perioperative and overall survival (OS) outcomes following CRS + HIPEC for isolated CRPM
- published between 1st January 2001 to 14th April 2020
- Manual cross referencing from bibliographies of papers in the initial search was done to include additional papers that had not previously been identified.

The exclusion criteria were as follow:

- Studies reporting on outcomes from appendiceal or non-colorectal cancers were excluded.
- studies reporting on multiple cancers were screened and excluded if data specific to CRPM could not be extracted.
- If institutional or multi-centred databases were published on more than one occasion, the study with the largest population or more relevant outcome was chosen.
- abstract form
- those on patients with synchronous liver resections & those with inadequate or absent perioperative or survival outcomes.

Outcomes after CRS and HIPEC:

i. Assessment of survival

Most of all 20 studies reported on OS. Overall median survival ranged from 14.6 to 60.1 months. This review reported that five studies show an overall median survival of more than 40 months and only six studies have shown survival less than 30 months.

By definition, a complete cytoreduction (CC) indicates that the surgeon has been successful in clearing all sites of visible disease (CC=0), or has left behind a minimal deposit less than 0.25 cm that are expected to be eradicated by HIPEC (CC=1). A CC score of 0 or 1 is considered complete.

Meanwhile, the peritoneal carcinomatosis index (PCI) score is another prognostic indicator established at the time of surgery. PCI is universally used to evaluate the extent of disease, communicate accurate disease burden between clinicians and act as a prognostic tool to predict patient survival. Out of 11 studies reported complete OS in patients CRS separately. A median survival for this group of patients ranged from 25 to 49 months with 3- year survival range in between range of 5% to 65% and the 5- year survival range in between 23.4% to 52%. The median disease-free survival (DFS) ranged from 9.5 to 18.5 months. Lastly, majority of the studies reported about the morbidity and majority in 17/20 studies with showed in their grade III/IV morbidity and mortality rates. Major morbidity ranged from 15.1% to 47.2% and mortality ranged from 0 to 4.5%.

The authors concluded that CRS+HIPEC in combination with systemic modern chemotherapy regimens is safe and feasible for the management of CRPM.

Narasimhan V et al. in 2020 conducted a SR with MA of non-RCTs studies with aimed to evaluate prognostic factors influencing survival in patients undergoing CRS and HIPEC for isolated colorectal peritoneal metastases (CRPM). In this review consist of multi-centre nine studies with 24 being single-institution studies of fair quality and 33 studies were eligible and included in the SR. A total number of participants of 4988 patients with 25 studies included in the pooled meta-analysis.

Among the prognostic factors influencing the overall survival are, as follow:

1. Location of primary tumour

There are three studies (n=254) reported the impact of primary tumour location. From the pooled results demonstrated that the rectal primary leading to peritoneal metastases was associated with a significantly worse survival than a colonic primary (HR: 1.93, 95% CI 1.10 to 3.37, $p = 0.02$, $I^2 = 0\%$)

2. Timing of onset of peritoneal metastases

In this pooled meta-analysis studies which included of (n= 366) patients, evaluated the difference in survival between synchronous or metachronous presentation of peritoneal metastases. The findings showed that there is no difference in survival based on timing of onset of peritoneal metastases. (HR 1.02, 95% CI 0.59 to 1.73, $p = 0.96$, $I^2= 50\%$) and its classified as moderate heterogeneity.

3. Grade III/IV morbidity

Four studies with a total number of 717 patients were evaluated the effect of perioperative grade III/IV morbidity on OS. The pooled results showed that the presence of grade III/IV morbidity was independently associated with worse OS, (HR 1.59, 95% CI 1.17 to 2.16, p = 0.003, I2= 18%) and its classified as low heterogeneity

4. Completeness of cytoreduction or better known as CC=0/1

Eight studies with a number of patients (n=1675) were evaluated the completeness of cytoreduction on survival after CRS + HIPEC and the results from the pooled results indicated that the incomplete CC was associated with a significantly worse survival (HR 2.21, 95% CI 1.57 to 3.10, $p < 0.001$), with $I^2= 46\%$) and to evaluate heterogeneity further, the largest weighted study by Elias et al. was removed and re-analysed, with a similar significant outcome, showing and classified it as low heterogeneity ($I^2 = 21\%$).

5. Peritoneal carcinoma index (PCI)

Eight studies were included in this outcome with a total number of patients (n=1279) showed that increasing PCI was associated with worse survival, with each unit increase in PCI contributing to a 10% increased hazard of death (HR 1.10, 95% CI 1.05 to 1.15, I2= 78%) and its classified as substantial heterogeneity.

6. Tumour differentiation

Only three studies (n=452) evaluated tumour differentiation as a prognostic factor and the results from the pooled results showed a poor tumour differentiation did not appear to confer a worse survival (HR= 1.91, 95% CI 0.72 to 5.07, I^2 = 72%) and classified as substantial heterogeneity

7. Lymph node positivity

Nine studies (n=1675) evaluated the effect of lymph node involvement of the primary tumour on OS after CRS + HIPEC and the results showed that the lymph node involvement was associated with a significantly worse OS (HR = 1.33, 95% CI 1.04 to 1.72, *p* = 0.03; Heterogeneity was moderate (I^2=31%). When Ung et al. excluded, the overall outcome remained the same, with no heterogeneity (I^2 = 0%).

8. Signet ring cell histology

Three studies (n=643) evaluated the role of signet ring cell histology on OS.
And the findings revealed no survival difference based on signet ring cell histology (HR= 1.11, 95% CI 0.65 to 1.90, *p* = 0.71, I^2 = 0%).

9. HIPEC drug

Four studies (n=1112) evaluated the survival benefit based on the HIPEC drug used and the results demonstrated that there was no difference in survival based on the HIPEC drug used (HR =1.00, 95% CI 0.65 to 1.53, *p* = 0.99) with substantial heterogeneity (I^2 = 70%).

10. Adjuvant systemic chemotherapy

Six studies (n=1372) evaluated the impact of adjuvant systemic chemotherapy following CRS + HIPEC. The use of adjuvant systemic chemotherapy was associated with an improved OS (HR= 0.71, 95% CI 0.54 to 0.93, p = 0.01), (I^2 = 43%) and classified as moderate heterogeneity.

The author concluded that in addition to completeness of cytoreduction (CC), increasing PCI & lymph node involvement, this meta-analysis demonstrates that primary tumour location, adjuvant chemotherapy and perioperative grade III/IV morbidity are also key prognostic factors influencing survival in patients undergoing CRS + HIPEC for isolated CRPM.

While CRS and HIPEC as a combined treatment has been demonstrated to be superior to systemic chemotherapy in CRPM, very few studies have evaluated the role of CRS alone without HIPEC. In an RCT by Elias et al. compared the use of early postoperative intraperitoneal chemotherapy (EPIC) plus systemic chemotherapy versus systemic chemotherapy alone in patients undergoing CC.

6.1.2 GYNAE-RELATED

Three SR were included in this review. (Kim Si, Cianci S and Tempfer CB).
Systematic review by Kim SI et al. in 2019 compared between adding the HIPEC procedures as a new intervention with a group of non-HIPEC. This review aims to identify patients with ovarian cancer who can obtain survival

benefit from HIPEC and to investigate the effect of HIPEC on the survival of patients with ovarian cancer. All studies in this review included OS and DFS as they measured outcomes and presented in a meta-analysis results with a total of 15 studies which consists of 13 case control studies and two RCTs. The total number of participants in this review was (n=1314). The inclusion studies are as follow:

- patients with epithelial ovarian cancer
- study designs included RCT, case-control, and 2-arm cohort studies; and comparison of DFS or OS between patients who underwent HIPEC or not

The exclusion criteria are:

- review articles, case reports, editorials, and letters to the editor; studies that had no data of survival or did not meet the selection criteria
- non-English paper

Results:

i. Effect of HIPEC on survival (OS) by study design (n=1314) demonstrated that potential confounding variables such as age, FIGO stage, histology, grade, and residual tumour size at the first surgery were adjusted in most of the studies. In all the studies, HIPEC found to be improved both DFS & OS as follows:

- DFS: (HR= 0.603; 95% CI 0.513 to 0.709)
- OS: (HR= 0.640; 95% CI 0.519 to 0.789 and
- the subgroup analyses confined to the case-control studies HIPEC improved: DFS: HR= 0.575; 95% CI, 0.471 to 0.702) and
- OS: HR= 0.613; 95% CI 0.398 to 0.944

ii. The effect of HIPEC on survival by disease status were reported in five studies with a total number of patients (n=630) showed that HIPEC was associated
with better DFS: HR= 0.580; 95% CI 0.476 to 0.706) and in another five studies (n=591) showed that HIPEC was associated with better OS: HR= 0.611; 95% CI, 0.376 to 0.992 and subsequently the subgroup analyses according to the study design, FIGO stage, and adjustment of confounding variables, HIPEC showed a favourable effect on DFS and failed to improve OS. This SR demonstrated that HIPEC showed a favourable effect on OS for advanced, stage III-IV disease with HR= 0.748; 95% CI, 0.563 to 0.994.

iii. The effect of HIPEC based on recurrent disease
There were five studies with a total number of patients of (n=357) included in this outcome. From the results did not show improved DFS after HIPEC: (HR= 0.644; 95% CI, 0.395 to 1.049). Subgroup analyses according to the study design and quality of study showed that in the group of HIPEC failed to improve DFS but showed better DFS after adjusting the confounding variables.

The result of OS for recurrent disease in seven studies (n=491) showed the survival benefit after HIPEC: HR= 0.566; 95% CI, 0.379 to 0.844 and after a

pooled meta-analysis in five studies that targeted platinum-sensitive recurrent disease showed a favourable effect on the OS: (HR= 0.616; 95% CI, 0.402 to 0.945) and subsequently the subgroup analysis showed that HIPEC was consistently associated with better OS. HIPEC did not increase OS of patients with no visible tumour: (HR= 0.564; 95%CI, 0.310 to 1.027) despite the improvement of OS of those with residual tumours ≤1 cm after CRS: HR= 0.591; 95%CI, 0.431 to 0.811 and subsequently the subgroup analysis showed that HIPEC was effective for patients with recurrent disease who had residual tumours ≤1 cm after CRS: HR= 0.493; 95%CI, 0.315 to 0.773

Cianci S et al. in 2020 performed a SR with MA from seven studies of observational studies with a total number of patients of 480 regarded women with ROC treated with or without HIPEC. The aims of this review is to explore whether the addition of the procedure of HIPEC in **recurrence ovarian cancer (ROC)** patients could improve the clinical outcome. Most of the studies were conducted in France, Spain, Italy, Israel, Brazil and Egypt between 2009 and 2019.

Results:

Effectiveness: Women with ROC:

In the group of CRS+HIPEC and chemotherapy demonstrated with a significantly improved 1-year OS when compared to group of without HIPEC = (OR= 2.42; 95% CI, 1.06 to 5.56; *p*=0.04; I^2 =4%). The outcome maintained significant and improvement in OS after 2-, 3- and 5- years respectively:

- 2-years OS: (OR 3.33; 95% CI, 1.81 to 6.10; p<0.01; I^2=0%)
- 3-years OS: (OR 4.22; 95% CI, 2.07 to 8.60; p<0.01; I^2 =52%)
- 5-years OS: (OR 5.17; 95% CI, 1.40 to 19.09; p=0.01; I^2 =82%)

In this study, the authors acknowledged that the perioperative mortality and complications were reported between day one and until 30 days after surgery in the group with additional HIPEC procedure, reported rates were:

- Baiocchi et al: 4%
- Amira et al: 13.3%
- No perioperative deaths (mortality) were reported in 4 studies
- Mean Length of stay (LOS)= 15.9 days (range 5.1 and 25.8)

Tempfer CB et al. in 2019 reviewed and conducted a SR with aim to summarise the available clinical data examining the role of HIPEC in patients with EC-derived PM undergoing CRS, in order to better define the safety and efficacy of HIPEC procedure. However, there were no meta-analysis was not possible due to the heterogeneity of studies. This review included eight studies with a small number of patients (n=68) which consist of one case report, one retrospective cohort study, one prospective cohort study, and five case series. The mean age of affected women was 57.1 years. The majority of patients had adenocarcinomas (41/64), with type II cancers including serous-papillary, clear cell, and carcinosarcomas were present in 23/64 patients. The mean (PCI at the time of CRS+HIPEC was 16.7 and a macroscopically complete surgical resection, i.e. CC= 0, in 44/63 which caters

for about 70% of included patients. Most of the chemotherapy regimens used for HIPEC were variable, but all included cisplatin, which was administered either alone (39/68 patients) or in combination with doxorubicin (DOXO) or paclitaxel (PAC) or mitomycin (MITO) (29/68 patients). The duration of HIPEC was between 60 - 90 min with majority of the procedures were using closed technique (55/68 patients).

Results:
From the study, the mean time from initial treatment of EC to CRS and HIPEC was in between of 22.3 months with the median DFS was 7 to 18 months and finally the median OS was reported as 12 to 33 months. Postoperatively, most patients also received systemic chemotherapy (46/63 patients).

6.1.3 OVARIAN CANCER

HIPEC as an adjuvant may improve DFS of patients with ovarian cancer when residual tumours were ≤1 cm or not visible. (DFS: HR= 0.580; 95% CI 0.476 to 0.706) HIPEC treatment also improved the prognosis in both primary and recurrent disease. However, the effect of HIPEC was not observed in patients with primary disease who had residual tumours ≤1 cm or no visible tumours. It may also improve OS of only patients with recurrent disease whose residual tumours were ≤1 cm. (OS: HR= 0.611; 95% CI, 0.376 to 0.99)

For women with recurrence ovarian cancer (ROC) and be treated with CRS+HIPEC and chemotherapy, OS showed a significantly improved 1-year OS when compared to protocols without HIPEC (OR 2.42; 95% CI, 1.06 to 5.56; p=0.04; I^2 =4%) and maintained significant improvement in OS after 2-, 3- and 5- years respectively. (2-years OS= OR: 3.33; 95% CI, 1.81 to 6.10; p<0.01; I^2=0%); 3-years OS: (OR 4.22; 95% CI, 2.07 to 8.60; p<0.01; I^2 =52%); 5-years OS: (OR 5.17; 95% CI, 1.40 to 19.09; p=0.01; I^2 =82%).

6.2 SAFETY

Five SR with or without MA were included in this outcomes. (Zhao ZY, Flood M, Narasimhan V, Cianci S and Tempfer CB) in various modalities of selected patients for such CRC, ovarian cancer and EC-derived PM. All selected studies were using CRS + HIPEC as the intervention and compared it with standard treatment of no HIPEC group as control.

Generally, CRS + HIPEC combined treatment offer an acceptability safety profile. in A modern chemotherapy regimens were introduced by using different chemotherapy agents with different toxicity. The most common adverse effects (AEs) such as nausea were similar to post chemotherapy procedure. Adverse events grade 1 and 2 were mostly observed in those patients compared to grade 3 and 4. Most of AEs reported could be resolved by standard care treatment such as anti-emetics. Treatment-associated mortality was reported as 1% (in EC-derive PM) and up to 4% in CRC PM.

Oxaliplatin showed a higher proportion of severe complications compared to mitomycin C (MMC) based as chemotherapeutic agents for HIPEC in patients with CRC PM.

6.3 ORGANISATIONAL

There are two main guidelines regarding HIPEC as an adjuvant therapy to CRS. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO). Both guidelines suggested a consideration in selection of patients with colon cancer and low-volume peritoneal metastasis, CRS and HIPEC at experienced centres may provide prolonged survival.

Currently, HIPEC is not considered as the standard of care in the management of either primary or recurrent EOC. Yet, it presents superior outcomes in selected clinical settings as demonstrated by RCTs. According to a survey conducted by the study group of Spiliotis et al and based on questionnaires answered by 467 Medical, Surgical and Gynecologic oncologists, the proportion of physicians who considered there is a utility of HIPEC in the management of primary and recurrent EOC was approximately 50% and 70%, respectively.

A critical question regards the optimal chemotherapeutic regimen as well as the ideal dose of the agent. There is a significant variety of drugs and drug combinations reported in the literature that are used for HIPEC. The most common chemotherapeutic regimens either as upfront or as secondary disease relapse therapy for HIPEC include cisplatin in doses ranging from 75 to 100 mg/m2, paclitaxel 175 mg/m2 alone or cisplatin plus paclitaxel. These regimens are suggested for patients with platinum-sensitive disease. Favourable outcomes have been also reported with administration of 35 mg/m2 doxorubicin and 175 mg/m2 paclitaxel or 15 mg/m2 mitomycin for platinum-resistant disease. To date, only cisplatin 100 mg/m2 has been included in the NCCN guidelines as a chemotherapeutic regimen for HIPEC in stage III disease after neoadjuvant chemotherapy (2). Nonetheless, the decisions regarding the preoperative, the postoperative and HIPEC chemotherapeutic regimens is not restricted to the NCCN recommendations. Other combinations of agents such as a paclitaxel containing HIPEC regimen are yet to be examined by randomised trials.

On the other hand, the chemotherapy solution is prepared in the pharmacy department and it is sent to the operating room in a closed light-protected bag with appropriate labelling which is handled with double gloves and the integrity of the bag is checked. Any leak detected results in the bag being returned to the pharmacy department. If the bag is approved there is no risk of direct exposure and it is given to the person responsible for the perfusion, who must check the patient’s name, drug and dose delivered against those prescribed.

Meanwhile, total procedure or operation time (median) varied widely based on surgeon techniques and experiences, ranging from 149.3 minutes (range 79-185 minutes) and hospital stay was 4.6 days (range 2-11 days) respectively.

Training for the specialised team and expertise is needed to conduct and initiate this combined treatment along with a proper radiation centre for handling the toxic waste and other measurement secured.

A designated operating room is needed for the smooth operating procedure when HIPEC treatment is introduced to a local MOH facilities.

6.4 ECONOMIC IMPLICATION

Overall, CRS and HIPEC treatment results in significant increases in medical costs with a parallel increase in survival for a disease that has been poorly treated, and hence may be considered as cost-effective given the observed life years gained. There were two studies on cost-analysis retrieved.

The first economic evaluations examined the cost effectiveness of CRS+ HIPEC compared with palliative chemotherapy for patients with peritoneal carcinomatosis from colorectal cancer (CRC PM) within the context of the Singaporean health care system.

Lee ZJ conducted and examined the cost-effectiveness of CRS+ HIPEC compared with palliative chemotherapy for patients with peritoneal carcinomatosis from colorectal cancer (CRC PM) within the context of the Singaporean health care system. In this study, they included patients with evidence of extra-abdominal and liver metastases and the patient-related inclusion criteria specified an ECOG status of 0 or 1 and fitness for surgery or chemotherapy.

Cost Assessment:

Tangible cost components were compiled to estimate the hospital cost, including the costs incurred during initiation of treatment and any subsequent admissions for associated complications and the management of disease progression. All cost figures used were the absolute cost values before any governmental or insurance subsidies.

Clinical costs consisted of components related to administrative fees including the doctors, allied health care, physiotherapist, and occupational therapist fees. Facility fees included the costs incurred by the use of operation theatre (OT) or the chemotherapy rooms during outpatient chemotherapy sessions. The OT costs were the costs incurred as a part of the surgery and the use of consumables during the surgery such as surgical equipment sets, sutures, and dressing sets. Procedure costs were the costs incurred out of the OT during wound dressings & setting of invasive lines such as the central venous catheters or intra-arterial lines. Ward care costs included the costs incurred during stays in the ICU, HDU, and general wards.

The average cost for CRS+HIPEC appears to be higher than for palliative chemotherapy (S$83,680.26 vs S$44,478.87). However, prolonged survival and lower readmission rates are enjoyed by this group of patients compared with a matched group of patients treated with palliative chemotherapy. With a

difference in median survival of 38 months, at a cost difference of S$37,939.97, the cost per life year attained in the CRS+HIPEC group was significantly lower than the cost per life year attained in the palliative chemotherapy group.

In another economic evaluation studies by Chua TC aimed to measure and describe the survival outcomes and healthcare cost associated with CRS and HIPEC for peritoneal surface malignancies (PSM) at a centralised tertiary institution in Australia. In this CEA study, patient selection consisted a selected group from June 2002 to June 2008 (six financial years) with a total of 159 procedures of CRS and HIPEC were performed in 136 consecutive patients with PSM at Sydney, Australia. The evaluation for suitability to undergo CRS+HIPEC procedures was made during a twice weekly meeting where patients were presented for discussion and imaging results CT scans, CT-angiogram of the liver and PET scans were studied. The inclusion criteria are only patients with agemore than18 and less than80 years old, with a good performance status (WHO)- Performance Status ≤2) and confirmed by histologic diagnosis of a PSM. Meanwhile, the exclusion criteria are all the patients with extra-abdominal metastasis were excluded.

The average cost of CRS and HIPEC per patient and per life year for appendix cancer is AUD $88,423 (range: AUD $23,933–AUD $299,145) and AUD $37,737/LY. Colorectal cancer is AUD $66,148 (range: AUD $26,079–AUD $409,666) and AUD $29,757/LY; for pseudomyxoma peri tonei is AUD $92,308 (range: AUD $11,562–AUD $501,144) and AUD $29,559/LY; for peritoneal mesothelioma is AUD $55,062 (range: AUD $23,261–AUD $94,104) and AUD $20,521/LY; and for other peritoneal surface malignancies is AUD $44,668 (range: AUD $31,592–AUD $70,026) and AUD $22,091/LY.

7.0 Limitations

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers.

8.0 CONCLUSION

The availability of evidence differs between targeted group of patients, origin of the disease, technique and chemotherapy agents use in the procedure. Due to high heterogeneity within the selected studies, meta-analysis was not done. There was fair to good level of retrievable evidence to suggest CRS and HIPEC treatment comparing to standard procedure and treatment, CRS alone and systemic chemotherapy alone. CRS and HIPEC gave a tolerable OS in general, better prophylactic and significantly reduced the incidence of peritoneal metastases. It does offer acceptability safety profile and may benefit patients according to the selection criteria of the patient’s profile; such as the type of cancer origin, perioperative selection, completeness of cytoreduction (CC), increasing peritoneal carcinomatosis index (PCI), lymph node involvement and chemotherapeutic agents involved.

9.0 RECOMMENDATIONS

Based on the above review, CRS and HIPEC treatment may be introduced and initiated as an adjuvant therapy with cytoreductive surgery (CRS) for the treatment of colorectal carcinomatosis peritoneal metastases (CRC PM) and other gynae-oncological diseases patients in selected centres in Ministry of Health (MOH) facilities, provided local expertise is available and refinement of selection criteria of the patients.

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11.0 APPENDICIES

Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

PTK-Bor-11

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

1.0 BACKGROUND INFORMATION

Peritoneal surface malignancy (PSM) is a cancer arising from or spreading to the peritoneal surfaces and its represent an advanced form of abdominal malignancies with a grim prognosis and quality of life.[1,2,3,4] It can be primary disease arising from the peritoneum or a secondary disease. Primary PSM is rare whilst secondary PSM is by far the most frequent.[4,5] Primary PSM such as malignant peritoneal mesothelioma (MPeM) is a rare aggressive tumour of the peritoneum and have a poor prognosis.[6,7,8] Secondary PSM is often cancers of the gastrointestinal tract, but it can be frequently arising from ovarian cancer and breast cancer.[4]

Annual incidence of MPeM has been reported to be 0.2 to 0.3 cases per 1,000 000 people per year, globally. In United State of America, MPeM reported of 200-400 new cases diagnosed annually and, its incidence is increasing and expected to reach a peak in 2020 in Europe.[9] Canada reported approximately 300 cases per year[10,11] meanwhile in Finland, the incidence of MPeM was 0.74 cases per 1,000 000 people per year and the median survival time after diagnosis was four months.[12] According to the French multi-institutional prospective study - Evoluation of Peritoneal Carcinomatosis or EVOCAPE 1 in 2000, the median survival in patients with MPeM was 5.2 months for those with advanced colorectal cancer, 3.1 months for those with advanced gastric cancer and, only 2.1 months for patients with pancreas cancer.[9,13] Specifically, mesotheliomas are the cancers with the lowest five-year survival estimates at only 6.6% according to Office for National Statistics, Cancer Survival in England (2018).[14]

The most common site of origin of this aggressive tumour arising from serous surfaces is pleura (65%-70%), peritoneum (30%), tunica vaginalis testis and pericardium (1%-2%). Mesotheliomas have a three basic histologic forms; epithelioid (the most frequent), sarcomatoid or mixed biphasic. The most frequently initial symptoms are abdominal pain (35%), abdominal swelling (31%), anorexia, marked weight loss, and ascites.[6]

Formerly, these types of malignancies were considered incurable conditions and have been regarded as a terminal condition for palliative care.[1] A well-known mentor, Dr. Paul Sugarbaker showed that surgical removal of visible tumour for MPeM combined with locoregional heated chemotherapeutic drugs improved the survival and quality of life of these patients.[7,14,15] Subsequencely, the treatment paradigm of PSM has thus evolved from one of palliation to one of using multimodality therapy in an attempt to bring about long-term survival to patients with an acceptable rate of morbidity.[3]

Cytoreductive surgery (CRS) encompasses a wide range of accepted complex oncologic procedures namely hepatectomy, pancreaticoduidenectomy (Whipple), esophagectomy, and from resection of one peritoneal nodule to multivisceral resection with peritoneal stripping. Therefore, these procedures reflect a wide range of possible morbidity.[8]

Cytoreductive surgery and hyper thermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal malignancies is practice at many centres and have been used as a standard but the literature is scarce in many aspects related to the management of CRS-HIPEC.[7] CRS-HIPEC is a standard combined treatment modality treatment for resectable tumours at diagnosis, is an aggressive locoregional treatment that has been available as a treatment option for peritoneal carcinomatosis since the mid-1990s.[6,8, 16, 17] The surgical procedure involves debulking and stripping of the diseased peritoneum and multiple visceral organ resections. Following the surgery, a heated chemotherapy is administered intraoperatively into the abdomen to cover all raw peritoneal surfaces. In 1990s, cytoreduction combined with intraperitoneal

chemotherapy was considered for patients with peritoneal mesothelioma. In addition, hyperthermia has been demonstrated to have a synergic effect with the chemotherapy and can thus enhanced the cytotoxicity of the drug.[18]

Technical Description of Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
Two different techniques for the delivery of HIPEC:

v. In closed techniques, inflow and outflow perfusion catheters are placed into the abdomen (intra-abdominally) and the skin edges are closed while
vi. in open techniques the skin edges are not approximated. Instead, the skin is secured to the abdominal retractors and plastic drapes and are sewn to the skin edges to act as a partial barrier to contain the chemotherapy solution and prevent heat loss.

Each technique has its advantages and disadvantages. In closed techniques, the surgeons may more easily maintain consistent intra-abdominal temperature. This technique offers less chance for chemotherapy spillage, and reduces the potential for toxic vapour escape into the room atmosphere. In open technique, the surgeons may better assure all the surfaces of the intra-abdominal organs are bathed by the chemotherapy solution, but the chances of spillage are greater and no assurances that chemotherapy vapours are properly evacuated.[3] More surgeons used a closed system with an FDA-authorised or commercially available perfusion machine for HIPEC.[19] The role for direct drug delivery to the peritoneal and tumour surfaces was described and reported in multiple review of cisplatin administration where the chemotherapeutic agents were delivered intraperitoneal at concentrations up to 30 times greater than those safely administered via intravenous route.[20]

Role of Hyperthermia
Hyperthermia alone is cytotoxic at the cell and tissue levels with formation of heat shock proteins.[20, 21] HIPEC combined the pharmacokinetic advantage inherent to the intra cavity delivery of certain cytotoxic drugs which results in regional dose of intensification, with the direct cytotoxic effect of hyperthermia. Hyperthermia exhibits a selective cell-killing effect in malignant cells by itself and enhances the tissue penetration of the administered drug.[22] HIPEC required the spread of cytostatic drugs during the surgical intervention at high temperature (41 – 43°C) within 60 to 120 minutes.[22, 23]
Perioperative management of CRS-HIPEC consist of:

- eligibility for the CRS-HIPEC procedure
- perioperative staging and assessment

In Malaysia, access to this treatment option is limited as it only available in our local health care facilities; at University Malaya Medical Centre and few of private hospitals. Hence, this health technology assessment (HTA) was requested by the former General Surgeon and Colorectal Specialist, Ministry of Health Malaysia to assess the efficacy, safety and cost-effectiveness of HIPEC on health outcomes in treating patient Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases.

2.0 POLICY QUESTION

Should hyperthermic intraperitoneal chemotherapy (HIPEC) as an adjuvant therapy with Cytoreductive Surgery (CRS) be initiated and structured in Ministry of Health facilities?

3.0 OBJECTIVES

3.1 To assess the effectiveness and safety of CRS-HIPEC in patients Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases compared with standard medical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone with regards to patient outcomes such as overall survival, progression-free survival, perioperative and postoperative mortality, health-related quality of life, quality adjusted life years (QALY) gained, and adverse events/complications.

3.2 To assess the economic impacts of using HIPEC treatment in patients with Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases compared with standard surgical treatment (CRS only), other comparatives surgical procedures and or systemic chemotherapy alone.

3.3 To assess the ethical, social, and organisational aspects related to HIPEC treatment.

Research Questions

i. How effective is HIPEC as adjuvant therapy with CRS compared with standard surgical procedures / treatment?
ii. Is HIPEC safe when used for adjuvant therapy?
iii. What is the economic, ethical, social, and organisational implication/impact related to adjuvant therapy CRS with HIPEC?

4.0 METHODS

4.1. Search Strategy

Electronic database will be searched for published literatures pertaining to CRS-HIPEC.

4.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database will be searched.
4.1.2 Additional literatures will be identified from the references of the retrieved articles.
4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
4.1.4 There will be no limitation applied in the search such as year and language.
4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

a. Population :
- Pseudomyxoma Peritonei
- Malignant Mesothelioma
- Peritoneal metastases
- advanced gastric cancer
- gynaecologic cancer

- Advanced gastric ca/stage IV = Peritoneal carcinomatosis?

b. Intervention : CRS plus HIPEC

c. Comparators :
- CRS alone
- Systemic chemotherapy alone

d. Outcome :

xiii. Effectiveness of survival rates/ overall survival/5-years survival rate
xiv. Safety
- adverse events
- minor/major complications

xv. Health-related quality of life
xvi. Economic impacts
xvii. Cost-effectiveness
xviii. Cost-utility
xix. Cost-benefit
xx. Organisational issues
xxi. Hospital utilisation (readmission, length of stay, and emergency department presentations)
xxii. Training or learning curve to perform the procedure
xxiii. Ethical issue
xxiv. Social implication (e.g. patient satisfaction)

e. Study design : HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), and economic evaluation studies

f. English full text articles

4.2.2 Exclusion Criteria

a. Study design : Animal study, laboratory study, cohort, case-control, cross-sectional studies, narrative review
b. Non English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The risk of bias of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) and The Cochrane Collaboration's tool for RCT.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

iv. Details of methods and study population characteristics
v. Detail of intervention and comparators
vi. Details of individual outcomes specified

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness associated with HIPEC as adjuvant therapy with CRS for the treatment of Pseudomyxoma Peritonei, Peritoneal Mesothelioma, peritoneal metastases (carcinomatosis) and other gynae-oncological diseases will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5.0 Report writing

6.0 References

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Appendix 3

Search Strategy:

1 MESOTHELIOMA/ (14143)
2 mesothelioma*.tw. (16381)
3 PERITONEAL NEOPLASMS/ (15314)
4 (carcinomatos* adj peritoneal).tw. (29)
5 (peritoneal surface adj1 malignanc*).tw. (382)
6 (peritoneal adj2 surface malignancy).tw. (191)
7 peritoneal neoplasm*.tw. (50)
8 (ascites adj1 gelatinou*).tw. (38)
9 PSEUDOMYXOMA PERITONEI/ (1024)
10 pseudomyxoma peritonei.tw. (1411)
11 (pseudomyxoma peritonei * adj2 syndrome).tw. (917659)
12 (pseudomyxoma peritonei adj2 syndrome*).tw. (43)
13 (syndrome adj3 pseudomyxoma peritonei).tw. (46)
14 ABDOMINAL NEOPLASMS/ (9434)
15 (abdominal adj1 neoplasm*).tw. (193)
16 COLORECTAL NEOPLASMS/ (89430)
17 (colorectal adj1 (cancer* or carcinoma* or tumor* or neoplasm*)).tw. (120123)
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (1091313)
19 HYPERTHERMIA, INDUCED/ (17207)
20 (therapy adj1 fever).tw. (243)
21 (hyperthermia adj1 (induced or local or therapeutic or intraperitoneal chemotherapy*)).tw. (3511)
22 (chemotherapy adj2 hyperthermic intraperitoneal).tw. (2130)
23 thermotherapy.tw. (2351)
24 (surgical procedure* adj2 cytoreducti*).tw. (33)
25 (cytoreductive adj1 (surger* or surgical procedure*)).tw. (5073)
26 (debulking adj2 surgical procedure*).tw. (17)
27 (procedure adj1 (cytoreducti* surgical or debulking surgical)).tw. (17)
28 HIPEC.tw. (2104)
29 Machine.tw. (87701)
30 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (112282)
31 18 and 30 (5079)
32 limit 31 to (english language and humans) (3592)