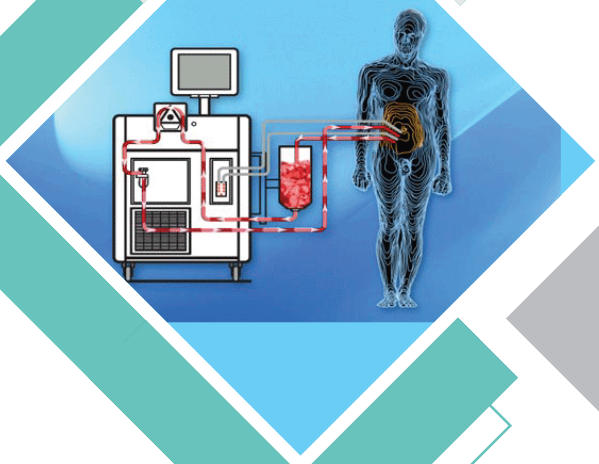
Ministry of Health
Directorate of Health Services

Health Technology Assessment Department



HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

HEALTH TECHNOLOGY ASSESSMENT REPORT

Ministry of Health
Directorate of Health Services

Health Technology Assessment Department

HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Health Technology Assessment Report

Ankara
STD 2018.01/00

March - 2018

The report is published under the responsibility belong to General Directorate of Healthcare Services, Department of Health Technology Assessment. The comments and ideas which are mentioned in the report may not reflect the official view of Ministry of Health, General Directorate of Healthcare Services.

Ministry of Health
Directorate of Health Services
Health Technology Assessment Department

ISBN: 978-975-590-672-0

I. PREFACE

The Health Technology Assessment (HTA) is that the technologies used in health services is examined and interpreted in terms of various aspects, and medicines, medical devices, medical treatment methods, surgical techniques, health care systems and similar applications are contained within the definition of health technology. The assessment of health technology is primarily conducted for clinical efficacy and patient safety; then a report is prepared via an economical analysis and by assessing the social and ethic aspects, as well as institutional aspects. Scientific evidences are based on all stages of HTA to which all relevant parties are contributed and that are carried out in a transparent process.

National HTA duty, power and responsibility had been assigned to Directorate General for Health Research (DGHR) with the provision of "Performing Assessments or Having the Assessments Performed about effectiveness, productivity, clinical, ethical, social, legal, organizational and economical effects of the protective, rehabilitating services, diagnosis and treatment methods; developing and generalizing evidence-based medicine applications and clinical guidelines" contained in the sub-paragraph (e) of the first paragraph of Article 12 under Decree Law No.663 on the Organization and Duty of the Ministry of Health and Its Affiliates. However, SAGEM has been closed and all ongoing projects have been hand overed to General Directoaret of Healthcare Services (DGHS) depending on Law 6569 TUSEB, Article 45 on 26.110217.

The Department of Health Technology Assessment (HTA) is within the structure of DGHS and is responsible for performing assessments or having the assessments performed in terms of the effectiveness, productivity, clinical, ethical, social, legal, organizational and economical effects of the protective, rehabilitating services, diagnosis and treatment methods in Turkey. The main policy of HTA Department in the health technology assessment process is to encourage the use of new or disregarded clinically effective health technologies in the health care services reasonably and equally and to prevent wastage in the health services by reducing the use of the health technologies having no clinical effectiveness and the financially non-sustainable health technologies with a clinical effectiveness.

HTA project/study on "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)" has been carried out in this context and accomplished as an HTA short report.

II. EXECUTIVE SUMMARY

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been used in the treatment of peritoneal site cancers since 1990. Cytoreductive surgery (CRS) is defined as the debulking of primary cancer and the cancer in the other visceral organs and peritoneal surfaces. The purpose of CRS combined with HIPEC is to excise all macroscopic diseases and to improve the patient's life span with chemotherapeutic agent treatments in the peritoneal cavity. Treatment is covered by the Social Security Institution (SSI) within the scope of "Annex 2B Fee For Service" since 2012 as per the tertiary health care providers affiliated to the Ministry of Health. Chemotherapy drugs (e.g. cisplatin, mitomycin, paclitaxel, cisplatin+doxorubicin, cisplatin+ mitomycin, etc.) used during treatment can be invoiced separately.

The object of this study is to study, assess and report HIPEC treatment using Health Technology Assessment (HTA), as a short report. Assessment will be done under the following titles in accordance with European Network for Health Technology Assessment (EUnetHTA) guidelines.

Literature Review was done with the given key words in the data libraries of Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar between January 1, 2017 and June 30, 2017. A total of 8.229 studies have been reached during the systematic review. Abstracts of these studies were assessed according to PICO criteria. 102 studies have been included the report depending on the review of specialist after the publish of draft report.

There are no treatment guidelines on which a full consensus has been reached and standardization in the treatment has not yet been established for HIPEC. In some countries, including Turkey, although the treatment is within the scope of reimbursement, the technology assessment process is still in progress.

A limited number of randomized clinical trials performed for evaluating clinical effectiveness of the HIPEC treatment with CRS in the treatment of peritoneal carcinomatosis demonstrate that this intervention improves the overall survival rates, survival rates in the first, second, third, fourth and fifth years, disease-free survival, and recurrence rates with correct patient selection. There are limited studies in ovarian cancer treatment. It is understood that a well-designed, multicenter, prospective, randomized clinical trials focusing on ovarian cancers are necessary, especially it

is not possible the results of in the treatment of gastric and colon cancers for the interpretation of the outcome of HIPEC in the treatment of ovarian cancers.

An important consequence of the literature review is that the reimbursed amount of cost does not meet the real costs and puts additional financial burden on the hospital, in the case that payments are done according to diagnosis-related groups (DRG) in two different countries (USA and Italy). One of the two studies, it has been stated that this is a cost-effective option given the severity of the disease and in the other study it has been indicated that it is not a cost-effective option due to cost-effectiveness rate is higher than reimbursement threshold.

Although there is not a cost effectiveness analysis conducted in Turkey, it has been observed that the HIPEC treatment has begun to be widespread in the light of General Directorate of Healthcare Services data. Cost data have begun to be created as it spreads. It has been observed in the light of the available data that the Ministry of Health adopts a policy which provides service under the reimbursement amount in order to improve health of the critically-ill patients. It is beneficial to carry out further cost-effectiveness analyzes in the light of the resulting data.

In the systematic literature analysis of HIPEC treatment with CRS in peritoneal carcinomatosis, it has been revealed that the main subject matters are the learning curve, the safety of treatment teams and the job descriptions when the subject matters discussed for the organizational aspects are considered. Studies have shown the importance of the learning curve and an improvement of the mortality and morbidity rates after a certain number of procedures have been reported.

Briefly, an analysis of studies examining the clinical effectiveness of HIPEC treatment with CRS in peritoneal carcinomatosis reveals that the intervention has a positive effect on both overall survival and quality of life with accurate patient selection and appropriate application.

III. PATIENT AND PATIENT DEPENDENT SUMMARY

The Health Technology Assessment (HTA) is that the technologies (medicines, medical devices, medical treatment methods, surgical techniques, health care systems and similar applications) used in health services is examined and interpreted in terms of various aspects, and are contained within the definition of health technology. The assessment of health technology is primarily conducted for clinical efficacy and patient safety; then a report is prepared via an economical analysis and by assessing the social and ethic aspects, as well as institutional aspects. Scientific evidences are based on all stages of HTA to which all relevant parties are contributed and that are carried out in a transparent process.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been used in the treatment of internal abdomen cancers since 1990. Cytoreductive surgery (CRS) is defined as the debulking of primary cancer and the cancer in the other internal organs and abdomen surfaces. The purpose of CRS combined with HIPEC is to excise all eye seen diseases and to improve the patient's life span with chemotherapeutic agent treatments in internal abdomen.

Treatment is covered by the Social Security Institution (SSI) within the scope of "Annex 2B Fee For Service" since 2012 as per the tertiary health care providers affiliated to the Ministry of Health. Chemotherapy drugs (e.g. cisplatin, mitomycin, paclitaxel, cisplatin+doxorubicin, cisplatin+ mitomycin, etc.) used during treatment can be invoiced separately.

The object of this study is to study, assess and report HIPEC treatment using Health Technology Assessment (HTA), as a short report. Assessment will be done under the following titles in accordance with European Network for Health Technology Assessment (EUnetHTA) guidelines.

Literature Review was done with the given key words in the data libraries of Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar between January 1, 2017 and June 30, 2017. A total of 8.229 studies have been reached during the systematic review. Abstracts of these studies were assessed according to PICO (scope) criteria. 102 studies have been included the report depending on the review of specialist after the publish of draft report.

There are no treatment guidelines on which a full consensus has been reached

and standardization in the treatment has not yet been established for HIPEC. In some countries, including Turkey, although the treatment is within the scope of reimbursement of some reimbursement agencies, the technology assessment process is still in progress.

A limited number of randomized clinical trials performed for evaluating clinical effectiveness of the HIPEC treatment with CRS in the treatment of internal abdomen cancers demonstrate that this intervention improves the overall survival rates, survival rates in the first, second, third, fourth and fifth years, disease-free survival, and recurrence rates with correct patient selection. There are limited studies in ovarian cancer treatment that is one of the female reproductive organs. It is understood that a well-designed, multicenter, prospective, randomized clinical trials focusing on ovarian cancers are necessary, especially it is not possible the results of in the treatment of digestive system and large bowel cancers for the interpretation of the outcome of HIPEC in the treatment of ovarian cancers.

An important consequence of the literature review is that the reimbursed amount of cost does not meet the real costs and puts additional financial burden on the hospital, in the case that payments are done according to diagnosis-related groups (DRG) in two different countries (USA and Italy). One of the two studies, it has been stated that this is a cost-effective option given the severity of the disease and in the other study it has been indicated that it is not a cost-effective option due to cost-effectiveness rate is higher than reimbursement threshold.

Although there is not a cost effectiveness analysis conducted in Turkey, it has been observed that the HIPEC treatment has begun to be widespread in the light of General Directorate of Healthcare Services data. Cost data have begun to be created as it spreads. It has been observed in the light of the available data that the Ministry of Health adopts a policy which provides service under the reimbursement amount in order to improve health of the critically-ill patients. It is beneficial to carry out further cost-effectiveness analyzes in the light of the resulting data.

In the systematic literature analysis of HIPEC treatment with CRS in internal abdominal cancers, it has been revealed that the main subject matters are the learning curve, the safety of treatment teams and the job descriptions when the subject matters discussed for the organizational aspects are considered. Studies have shown the importance of the learning curve and an improvement of the mortality (death) and

morbidity (illness) rates after a certain number of procedures have been reported.

Briefly, an analysis of studies examining the clinical effectiveness of HIPEC treatment with CRS in internal abdominal reveals that the intervention has a positive effect on both overall survival and quality of life with accurate patient selection.

IV. HEALTH TECHNOLOGIES ASSESSMENT PROJECT

IV.1. Scope, Method and Goal of the Project

Based on HTA study methods in the HTA project about "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)" ;

1. Health problem and current use of technology and description and technical features of the technology
2. Clinical effectiveness
3. Safety
4. Costs and economical assessment
5. Organizational aspects

were assessed.

The goal of the HTA project is to provide a scientific evidence-based support to healthcare providers, payers, decision-makers and policy makers through comprehensive and multi-faceted assessment of hyperthermic intraperitoneal chemotherapy treatment, to contribute to scientific literature in this field and to enhance the accumulation of scientific knowledge.

PICO of the HTA Project

Population/Problem/Patient Defines the population, problem and patient group for the research.	- In individuals with peritoneum metastasis or primary peritoneum cancer candidate for HIPEC treatment
Intervention Defines the intervention of the study for the population of the study.	- After cytoreductive surgery, intraoperative or postoperative hyperthermic intraperitoneal chemotheraphy (Hypertermic Intraperitoneal Chemotherapy – HIPEC) application
Comparator Defines the alternative(s) of the intervention of the study.	- Only cytoreductive surgery
Outcome(s) Defines the outcomes which will be assessed depending upon the alternatives of the intervention of the study.	- Overall Survival - Quality of Life Effect - Safety Side Effects - Mortality - Morbidity - Cost and cost-effectiveness - Organizational requirements

IV.2. Work Schedule

Work Schedule

The study on "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)" is a Health Technology Assessment study obtained by a short report assessment using HTA Core Model® for Medical and Surgical Interventions and the process have been started on 5 May 2017.

During the study process;

- A road map, PICO, methodology, systematic review keywords and review libraries were determined and systematic review was started with the meeting dated 26 May 2017.
- Road maps, PICO, methodology, systematic review keywords and review libraries were determined with the participation of relevant public institutions, clinicians, associations and private sector and were presented to stakeholders on 4 July 2017.
- The systematic review was terminated and the report preparation process was initiated on 21 July 2017.
- Assessment meetings were held between July and October 2017.
- The draft report was finalized and published on 27 October 2017.
- Reviews about draft report has been taken up to 16 November 2017.
- Reviews was evaluated and draft report was updated as final report on 25 December 2017.

IV.3. Participants, Stakeholders and Responsibility

Participant Institutions

	Institution	Role in the HTA Project
1	DGHR/DGHS	Project owner and coordinator, Editor, Coordinator, Author
2	DGHS	Researcher
3	SSI	Contributors
4	TPHI	Contributors
5	TPHGD	Contributors
6	TMMDA	Contributors
7	Universities	Contributors
8	Non-governmental Organizations	Contributors
9	Hasta/Hasta Yakınları	Contributors
10	Companies	Contributors

Stakeholders

	Persons/Institutions	Role in the HTA Project
1	Institutions - Public - Private	Stakeholder
2	NGOs - Professional Organizations - Associations - Foundations	Stakeholder
3	Companies - Drug - Medical device	Stakeholder
4	Patients Patients' Relatives	Stakeholder

Responsibility

All rights and responsibilities of HTA project on "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)" and the HTA Report to be published at the end of the process belong to DGHS.

IV.4. Systematic Review

Systematic literature review was done with the following key words in the data libraries of Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar between 2007 and 2017,

Hyperthermic Intraperitoneal Chemotherapy «and/or»

- Effectiveness
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Safety
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Colon Cancers
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Ovarian Cancers
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Pseudomyxoma Peritonei
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Malignant Mesothelioma
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Cost-Effectiveness
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Health Technology Assessment
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar)
- Organization
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Turkey
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar)

A total of 8.229 studies have been reached during the systematic review. Abstracts of these studies were assessed according to PICO criteria.

The result of the assessment was reported in the below:

- A total of 131 abstracts were reached on Ulakbim.
- A total of 51 abstracts were reached on Embase.
- A total of 161 abstracts were reached on Pubmed.
- No abstract was found with the key words on Cochrane, but only 2 abstracts were reached with Hyperthermic Intraperitoneal Chemotherapy review, and full texts of these abstracts were selected.
- No abstract was found with the key words on Turkey Citation Index.
- A total of 7884 abstracts were found on Google Scholar.
- As a result of duplication of 8.229 studies in total obtained via Ulakbim, Embase, Pubmed, Cochrane, Turkey Citation Index And Google Scholar, and first assessment carried out via the abstracts in accordance with PICO criteria, a total of 183 full texts were subjected to the second selection process.

The second selection was carried out with more detailed assessment of the PICO criteria on full texts. As a result of this assessment, a total of 101 full texts from 183 full texts were selected as articles to be the basis for the study.

IV.5. Project Team

In HTA study on "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)", project team and their duties are listed below. As the project team is created with a dynamic understanding, new participants have been added in the context of the need in the study process.

- Project Manager: Main responsibilities are to provide an administrative approval for the initiation of the HTA project titled "Hyperthermic Intraperitoneal Chemotherapy (HIPEC)" and publication of the final HTA report at the end of the process.

- Project Coordinator: Main responsibilities are making all organizations related to the HTA project, combining the section texts resulting from the study together with the author, making revisions, putting the HTA report into the final form, publishing HTA Report and releasing the same to the public and the relevant parties.

- Author: The main responsibility is planning of the activities required to be written such that it will answer the questions in the HTA Core Model® assessment component table for Medical and Surgical Interventions in the context of a short report in accordance with the division of labor determined by the Project Coordinator.

IV.5. Project Manager, Project Coordinator, Author, Contributors:

Project Manager:

- M. Rifat KÖSE (General Manager, Attending Physician)
- Bilgehan KARADAYI (Head of Department, Attending Physician)

Project Coordinator:

- Adile Acar (Communication Specialist/Researcher)

Project Author:

- Güvenç Koçkaya (Individual Consultant, Physician)

Contributors of the Project

	NAME-SURNAME	INSTITUTION
1	Prof. Dr. Hüseyin Koray TOPGÜL	Medical Park Hospital
2	Prof. Dr. Selman SÖKMEN	Dokuz Eylül University, Medical Faculty Department of General Surgery
3	Dr. Cihan AĞALAR	Dokuz Eylül University, Medical Faculty Department of General Surgery
4	Assoc. Prof. Dr. Salih TAŞKIN	A.U. Medical Faculty Department of Gynecology and Obstetrics
5	Assist. Prof. Gülpembe ERGİN OĞUZHAN	Ondokuz Mayıs University, Faculty of Health Sciences Department of Healthcare Management
6	Uzm. Dr. Bülent AKSEL	Dr. Abdurrahman Yurtarslan Oncology Training and Research Hospital
7	Fatma Betül YENİLMEZ, MSN	Health Economics and Policy Association
8	Filiz ÇAVUŞ ŞEN	Health Economics and Policy Association
9	Assoc. Prof. Dr. Sedat BOSTAN	Organization of Patient Rights
10	Mehmet Ali ÖZER	TOBB Medical Council
11	Prof. Dr. Ahmet ÖZET	TÜSEB
12	Dr. Ali Kemal ÇAYLAN	TKHK Financial Analysis Depoartment
13	Ali GÜL	TKHK Financial Analysis Depoartment
14	İsmet DEDE	THSK Cancer Department
15	Seda KUTLUER	SGK Health Resource Management Department
16	Uzm. Dr. İnci YANIKOĞLU	SGK Healthcare Services Department
17	Ali Rıza DEMİRBAŞ	Hospital Manager, DGHR/DGHS
18	Aysel ATEŞ	Health Administration Specialist, DGHR/DGHS
19	Elife DİLMAÇ	Health Administration Specialist, DGHR/DGHS
20	Gülcan TECİRLİ	Economist, DGHR/DGHS
21	İlker L. SABUNCUOĞLU	Physician, DGHR/DGHS
22	Mustafa KILIÇ	Health Economist, DGHR/DGHS
23	Olgun ŞENER	Public Management Specialist, DGHR/DGHS
24	Sevil AKDENİZ	Children Development Specialist, DGHR/DGHS

IV.6. Conflict of Interest Statement

Team members of HTA project about “Hyperthermic Intraperitoneal Chemotherapy (HIPEC)” have stated that they conducted the study without any material or moral influence that could be adversely affect the scientific view of the study, or without any relationship based on self-interest and they signed the conflict of interest statement (declaration of neutrality) contained in Annex-2.

V. TABLE OF CONTENTS

VI. LIST OF TABLES

VII. LIST OF FIGURES

VIII. ABBREVIATIONS

USA	**:** United States of America
AUD	**:** Australia Dollars
CC	**:** Completeness of Cytoreduction
DRG	**:** Diagnosis-Related Groups
ECOG	**:** Eastern Coopertive Oncology Group
EPIC	**:** Postoperative Intraoperative Chemotherapy
EUnetHTA	**:** European Network for Health Technology Assessment
CI	**:** Confidence Interval
HIPEC	**:** Hyperthermic Intraperitoneal Chemotherapy
ACER	**:** Additional Cost Effectiveness Ratio
PCI	**:** Peritoneal Carcinomatosis Index
PICO	**:** Patient Indicator Comparator Outcome
OR	**:** Odds Ratio
QALY	**:** Quality Adjusted Life Years
RR	**:** Relative Risk
SSI	**:** Social Security Institution
DGHS	**:** Directorate General for Health Services
CRS	**:** Cytoreductive Surgery
HTA	**:** Health Technology Assessment
DGHR*	**:** Directorate General for Health Research
TPHI**	**:** Turkish Public Hospitals Institution
TPHEI***	**:** Turkish Public Health Institution

***DGHR:** *"This study has been started under responsibility of SAGEM. However, SAGEM has been closed and all ongoing projects have been hand overed to SHGM depending on Law 6569 TUSEB, Article 45 on 26.110217. As a result, "HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)" HTA Report has been accomplished under SHGM HTA Department.*

****TPHI:** *"Has been included under Ministry of Health Center Orhanization and named as General Management of Public Hospitals by 694th Decree on the Implementation of Certain Regulations in the Context of the Emergency State.*

***** **TPHEI:** *"Has been included under Ministry of Health Center Orhanization and named as General Management of Public Health by 694th Decree on the Implementation of Certain Regulations in the Context of the Emergency State.*

1. Introduction

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been used in the treatment of peritoneal site cancers since 1990. Cytoreductive surgery (CRS) is defined as the debulking of primary cancer and the cancer in the other visceral organs and peritoneal surfaces. The purpose of CRS combined with HIPEC is to excise all macroscopic diseases and to improve the patient's life span with chemotherapeutic agent treatments in the peritoneal cavity. Treatment is covered by the Social Security Institution (SSI) within the scope of "Annex 2B Fee For Service" since 2012 as per the tertiary health care providers affiliated to the Ministry of Health. Chemotherapy drugs (e.g. cisplatin, mitomycin, paclitaxel, cisplatin+doxorubicin, cisplatin+ mitomycin, etc.) used during treatment can be invoiced separately.

The object of this study is to study, assess and report HIPEC treatment under the following titles using Health Technology Assessment (HTA), as a short report. Assessment will be done under the following titles in accordance with European Network for Health Technology Assessment (EUnetHTA) guidelines:

1. *Health problem and current use of technology and description and technical features of the technology*
2. *Clinical effectiveness*
3. *Safety*
4. *Costs and economical assessment*
5. *Organizational aspects*

In this context, the methodology of the study is discussed in the second section and in the following sections, the questions contained in the assessment components table of Health Technology Assessment Core Model for Medical and Surgical Interventions published by EUnetHTA are answered by the results of the systematic literature review and the clinical effectiveness, safety, cost and organizational aspects of the technology (HIPEC) have been assessed and reported.

2. Methodology

As stated above, the short technology assessment report created for this study is based on the approach suggested in the EUnetHTA core model. A systematic literature review was conducted in 2017 to reach the resources to be used for preparing the report. The systematic literature review was limited only to studies conducted on human being and resources in Turkish and English.

Literature Review was done with the following key words in the data libraries of Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar between January 1, 2017 and June 30, 2017,

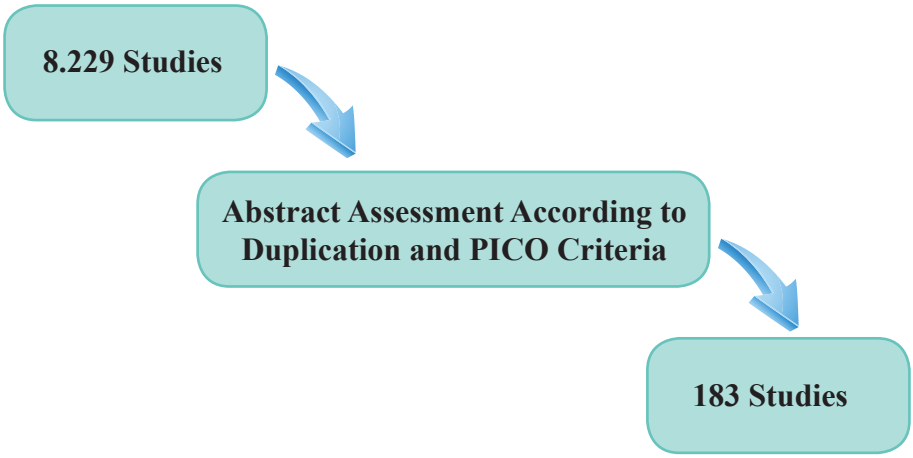
Hipertermic Intraperitoneal Chemotherapy «and/or»

- Effectiveness
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Safety
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Colon Cancers
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Ovarian Cancers
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkiye Atif Dizin
- Pseudomyxoma Peritonei
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Malignant Mesothelioma
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Cost-Effectiveness
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Health Technology Assessment
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar)
- Organization
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index)
- Turkey
  (Ulakbim, Embase, Medline, Pubmed, Cochrane, Turkey Citation Index, Google Scholar)

A total of 8.229 studies have been reached during the systematic review. Abstracts of these studies were assessed according to PICO criteria. The result of the assessment was reported in the below:

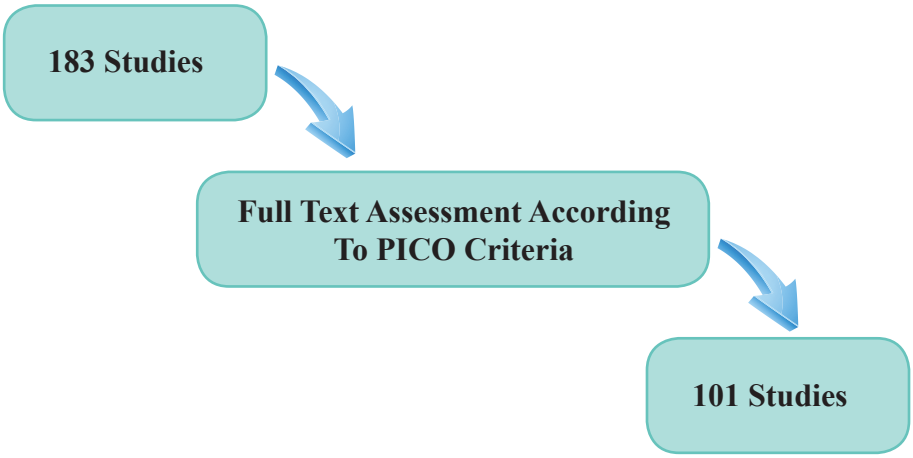
- A total of 131 abstracts were reached on Ulakbim.
- A total of 51 abstracts were reached on Embase.
- A total of 161 abstracts were reached on Pubmed.
- No abstract was found with the key words on Cochrane, but only 2 protocols were reached with Hyperthermic Intraperitoneal Chemotherapy review, and full texts of these protocols were selected.
- No abstract was found with the key words on Turkey Citation Index.
- A total of 7884 abstracts were found on Google Scholar.As a result of duplication of 8.229 studies in total obtained via Ulakbim, Embase, Pubmed, Cochrane, Turkey Citation Index And Google Scholar, and first assessment carried out via the abstracts in accordance with Patient Indication Comparator Outcome (PICO) criteria, a total of 183 full texts were subjected to the second selection process (Figure 1).

Figure 1: Results of Abstract Assessment of HIPEC Systematic Literature Review



The second selection process was performed by a detailed assessment of PICO criteria on the full texts. As a result of this assessment, 101 full texts out of 183 full texts were selected as the basis of the study (Figure 2) (ANNEX 1).

Figure 2: Results of Full Text Assessment of HIPEC Systematic Literature Review



Additional to the final 101 studies, 1 study which was reported by specialist under the review process of draft report has been included for final report. Totally 102 studies were reported in the following sections by an assessment carried out within the scope of the questions determined in HTA Core Model.

3. Use of Hyperthermic Intraperitoneal Chemotherapy as a Treatment Method

3.1. Introduction

In this section, information on the use of HIPEC will be presented within the scope of the results obtained as a result of systematic literature review. As part of the methodologic approach as explained in more detail in the section, the answers of the questions contained in the first section titled “Health Problem and Current Use of Technology” in HTA Core Model.

3.2. Assessments

HIPEC combined with CRS is an improved method from the early 1990s for the treatment of peritoneal surface malignancies. This malignancy may be a primary disease caused by peritoneum (such as malign peritoneal mesothelioma) or may be caused by the progression of primary cancers such as gastric cancer, colorectal cancer, ovarian cancer, appendicitis cancer, pseudomyxoma peritonei [1]. In peritoneal carcinomatosis, general survival rate is low, prognosis is poor and alternative therapy is only CRS application or chemotherapy. In this study, the HIPEC treatment in combination with CRS is assessed for the treatment of peritoneal carcinomatosis developed due to primer or any type of cancer.

The usage frequency of the treatment, or the number of patients using the treatment in HIPEC treatment combined with CRS is proportional to the progression of underlying malignancy and the fact that it causes peritoneal carcinomatous. Thus, the number of patients is proportional to the incidence of the underlying type of cancer. Gastric cancer is the second most common cancer type that causes death in the World after lung cancer, and is a malignant type of cancer, the prognosis of which is poor. [2,3]. Colorectal cancer is the third most common type of cancer in the world and 1.4 million new cases were diagnosed in 2012. According to predictions, the expected incidence in 2035 is 2.4 million. It is stated that 15% of patients diagnosed with colorectal cancer have peritoneal carcinomatosis during diagnosis and only 6 months of survival can be achieved in these patients [4]. In addition, it is also stated that 30% of patients diagnosed with primary colorectal cancer and 44% of recurrent patients develop peritoneal carcinomatosis [5]. Peritoneal carcinomatosis is the second cause of death in colorectal cancer patients [6]. 15-50% of gastric cancer patients develop peritoneal

carcinomatosis of various stages during the first diagnosis, but this rate develops around 35-50% in postoperative recurrence. All epithelial ovarian cancers beyond stage IIB develop peritoneal carcinomatosis as a natural development of disease progression. In peritoneal carcinomatosis, the median survival of the disease was 9 months before 1989, but nowadays long term survival is possible in 25-85% of the patients by surgical interventions depending on the patient and disease characteristics [1].

During the last thirty years, with the better understanding of tumor biology and the advancement of treatment technologies, significant changes have been occurred for the information on peritoneal carcinomatosis diseases, and these diseases are now being recognized as regional diseases rather than being considered as wide-spread metastases. Along with this change in the perception of the disease, target-specific therapies have begun to be developed, and the HIPEC combined with CRS is one of them. With this treatment method, it is possible to surgically remove large tumors that can be seen and to eradicate non-seen free tumor cells with micro-metastases [7]. Surgical intervention may cause some microscopic residual disease to remain in the abdominal cavity and visceral organs and in these situations, systemic chemotherapy after surgery may not be effective because of the weak penetration of these drugs into these points. Cytotoxic drugs diluted with 5% dextrose or saline are injected into the abdominal cavity and heated at 42-42,5°C for 30-90 minutes by HIPEC developed for these situations. The surgeon is able to manipulate visceral organs during the procedure to ensure homogeneous distribution of cytotoxic drugs between abdominal cavity and organs [8].

Peritoneal carcinomatosis index (PCI) developed by Sugarbaker is used for patient selection in accordance with HIPEC treatment combined with CRS. Accordingly, the abdomen is divided into 13 regions and the total score of each region constitutes PCI (Figure 3). PCI score is one of the important criteria for choosing the appropriate scoring for the treatment, and as it can be seen in the clinical effectiveness section below, better results can be obtained for survival and morbidity indicators if this score is ≤20.

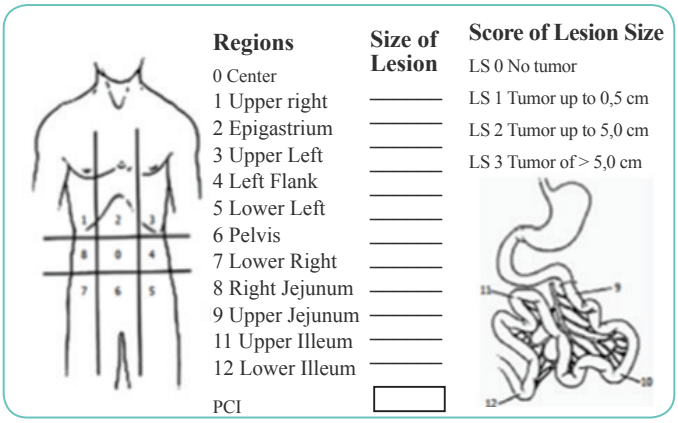


Figure 3: Staging System of Peritoneal Carcinomatosis Index [9]

The magnitude of CRS is an important indicator for assessing both treatment success and adverse events and survival in HIPEC treatment with CRS. The classification developed by Sugarbaker (1996) [10] and showing the Completeness of Cytoreduction (CC) is one of the most important determinants of general survival. Accordingly, a CC-0 score indicates that there is no residual peritoneal disease after CRS; CC-1 indicates a residual disease of <2,5 mm; CC-2 indicates a residual tumor between 2,5 mm and 2,5 cm; and CC-3 indicates a residual tumor of >2,5 cm or non-resectable tumor nodules.

Special equipment used in the treatment of HIPEC with CRS is presented as follows:

1: Device for HIPEC

2: Drugs used for HIPEC

Figure 4: Special equipment used for HIPEC[11]

HIPEC is applied after cytoreductive surgery (CC-0/CC-1) in the operating room and can be performed by an open or close technique. In the open method, coliseum technique is applied and four-vacuum drains are placed on the abdominal wall. The wound is partially covered with a plastic cover to prevent leakage and evaporation of abdominal fluids. During HIPEC application, a slit is made on the cover to allow the surgeon to access the abdomen and pelvis. A smoke evacuator is placed under the plastic cover to evacuate the chemotherapy vapors and small droplets. During the 30 min to 90 min of perfusion, the surgeon performs an intervention manually, so that a better and direct manipulation inside the abdomen is possible. However, in this way both the possibility of environmental contamination and the possibility of the surgeon being affected by chemotherapeutic agents increase. In the closed HIPEC technique, once the cytoreduction is completed, one or two in-flow and out-flow catheters are placed. Upon proper positioning of the thermal probes, the abdominal cavity is covered with a preheated solution after the skin is temporarily closed. The abdominal cavity is manually externally stimulated as the perfusate accumulation can later cause morbidity. After completion of perfusion, perfusate is emptied and is now filled with saline to remove chemotherapy. Although this method provides safety for surgeons, there may be no homogeneity in the distribution of heat and chemotherapy because no direct intervention can be done in the abdominal cavity [12]. According to Canada HIPEC Collaborative Group guidelines, both techniques are safe. However, the time and perfusion level should not be changed regardless of which technique is used.[1]. A synergistic effect is seen by using hyperthermia together with the chemotherapy at 42°C [7].

The chemotherapeutic regimens used in HIPEC differ from the centers where the application is carried out, without a standard approach. Among these are mitomycin, cisplatin, carboplatin, oxaliplatin, docetaxel, paclitaxel and fluorouracil [7]. The following table shows the chemotherapeutic agents that can be used in intraperitoneal chemotherapy.

Table 1: Cytotoxic Agents Used in Intraperitoneal Chemotherapy [13]

Drug	Class	Diluent	Heat Energy	Stability at Room Temperature
Doxorubicin	Anthracycline antibiotics	1,5% dextrose dialysis solution	Yes	7 days
Melphalan	Alkylating Agent	0,9% sodium chloride	Yes	2 hours
Mitomycin C	Antibiotic	1,5% dextrose dialysis solution	Yes	1 hour in perfusate
Cisplatin	Alkylating Agent	0,9% sodium chloride	Yes	20 hours
Gemcitabine	Pyrimidine antagonist	0,9% sodium chloride	Yes	Stabile
Mitoxantrone	Antibiotic	0,9% sodium chloride	Yes	7 days without dilution
Oxaliplatin	Alkylating Agent	5% dextrose	Yes	6 hours
Paclitaxel	Antimitotic	1,5% dextrose dialysis solution	No	27 hours
Etoposide	Topoisomerase Inhibitor	5% dextrose	Yes	24-96 hours

According to Canada HIPEC Collaborative Groups [1], the most commonly used chemotherapeutic agents are oxaliplatin and mitomycin C. The dose of oxaliplatin recommended in the clinical guideline is 460 mg/m^2 perfused for 30 minutes at 43°C. Systemic 5-fluorouracil and leucovorin may be administered by an anesthetist to increase the effectiveness of oxaliplatin. 5-fluorouracil should be administered intravenously for 30 minutes at a dose of 400-450 mg/m^2 30-60 minutes before HIPEC. Leucovorin should be administered intravenously at a dose of 20mg/m^2 for 10 minutes before 5-fluorouracil. Mitomycin C should be given with two syringes at a dose of 40 mg according to American guidelines. When mitomycin is used for HIPEC, subsequent systemic chemotherapy is not required. Table 2 presents the recommended agents and doses according to Canadian guidelines [1].

Table 2: Chemotherapeutic Agents and Doses Thereof Recommended According To Canada Guideline of HIPEC with CRS [1]

Drug	Dose	Time (Minute)	Intraabdominal Temperature (^{0}C)	Accompanying Intravenous Treatment
Oxaliplatin	300 mg/m^2 400 mg (fixed dose) 460 mg/m^2	30 60 30	40-43 40-43 40-43	5-F (400-450 mg/m^2) plus leucovorin (20mg/m^2) administered 30-60 minutes before oxaliplatin
Mitomycin C	10-30 mg/m^2 30-40 mg (fixed dose) 1mg/kg (max 70mg)	60-90 60-90 60-90	40-43 40-43 40-43	None None None

There are still some academically drawbacks regarding the use of HIPEC as a standard treatment. In a study by Braaam et al. [14], it was aimed to reveal the opinions of physicians on HIPEC in combination with CRS for the treatment of colorectal cancer patients with peritoneal metastases. In the study, 459 oncologic surgeons and 363 oncologists from the Netherland were applied a questionnaire via the internet and were asked to deliver their opinions about the treatment. The response rate to the study was 23% and 65% of the participants stated that there was sufficient evidence that the CRS + HIPEC treatment was effective and that this treatment was an effective treatment. 29% of the participants stated that although there was not sufficient evidence, the treatment was effective, while 7% indicated that treatment was probably not effective. While 74% of general surgeons have been mentioned in the study that there are enough evidence, 51% of medical oncologists have been reported there is not enoguh evidence for clinical evaluation. 68% of the participants describe CRS + HIPEC treatment as being the standard treatment for colorectal cancer treatment with peritoneal metastasis, while 30% do not consider this treatment as a standard treatment. The authors concluded that despite it is recommended in Dutch clinical guidelines, CRS + HIPEC treatment in the colorectal cancer treatment should be introduced to be accepted among physicians [14].

A limited number of national guidance development studies have been conducted in HIPEC treatment combined with CRS. A guideline to the use of HIPEC treatment combined with CRS in peritoneal surface malignancies due to colorectal

or appendicular neoplasms was developed by the Canadian HIPEC Collaborative Group, a group of Canadian medical and surgical oncology specialists [1]. In the guideline, the characteristics of patients who are eligible for HIPEC treatment in combination with CRS, have been indicated (Table 3). Accordingly, patients should not have any additional significant accompanying disease and the Eastern Cooperative Oncology Group (ECOG) performance status should be 0. In particular patients with a performance status of 1 among patients whose performance status can be corrected are also eligible for the treatment. Physiologic age must be taken into account and patients below 65 years of age should be considered as candidates for the treatment. Among the patients above this age, patients with low peritoneal carcinomatosis index and low grade tumors, who do not have accompanying disease should be included in the treatment. The body mass index should also be considered and the body mass index above 35 should be considered as a contraindication.

Table 3: Patient Selection Criteria According to Canada Guideline of HIPEC with CRS [1]

Criterion	Colorectal	Appendicular
ECOG Performance Status		
0	Yes (A)	Yes (A)
1	No (C)[a]	Yes (B)
2	No (A)	No (C)[a]
Patient Age		
≤ 65	Yes (A)	Yes (A)
66-74	No (C)[a]	No (C)[a]
≥ 75	No (B)[a]	No (B)[a]
Body Mass Index		
≤35	Yes (A)	Yes (A)
≥40	No (B)[a]	No (B)[a]
Histological Grade[b]		
Classic I or II	Yes (A)	Yes (A)
Classic III	No (B)[a]	
DPAM/LAMN/PMCA-I		Yes (A)
Classic III or PMCA		No (B)[a]
Time Elapsed from Primary Tumor to Peritoneal Carcinomatosis		
Any	Yes (A)	Yes (A)
≥6 months	No (C)[a]	
Simultaneous or <6 months		
Extraperitoneal Disease Exists[c]	No (A)	No (A)
Peritoneal Carcinomatosis Index		
Any		Yes (B)
≤20	Yes (A)	
>20	Yes (B)	
The Expected Score for Complete CRS		
	Yes (A)	Yes (A)
0	No (B)	Yes (A)
1	No (A)	No (C)[c]
2		No (A)
3		

[a] Up to 3 resectable liver metastasis.
[b] Points to classical, adenocarcinoma grades I-III.
[c] Usually a relative contraindication, may be thought according to patient and disease factors. It is recommended for the patient to be directed to a specific center.
Consensus degrees of physicians: (A)= >70% consensus, (B)= 50-70% consensus, (C)=< 50% consensus, (D)= Not suitable

The characteristics of the disease to be sought in the patients suitable for the HIPEC treatment combined with CRS according to the guideline developed by the Canadian HIPEC Cooperation Group differ depending on the primary tumor (origin of the tumor), the tumor histology (and tumor biology) and the extent of the disease. Histology should be determined by biopsy where appropriate, and the extent of the disease should be determined by laparoscopy or, in some cases, laparotomy, prior to surgery. The peritoneal cancer index should be used when defining the extent of the disease. Treatment is contraindicated in the case of additional histologically proven disease, three liver metastases (Q28, Q32, Q35; LOC A) and unknown primary tumors with N3 lymph nodes. The following tests and procedures should be performed while the disease is being evaluated [1]:

- Patient's detailed history and physical examination
- Appropriate blood tests (carcinoembryonic antigen in non-mucinous disease)
- Total colonoscopy
- CT scan for breast, abdomen and pelvis
- PET scan (in non- mucinous cases)
- Confirmation of diagnosis (pathological report, tissue biopsy or progression on the scan)
- Other tests such as laparoscopy, as needed

Another guideline study was conducted by the American Society of Peritoneal Surface Malignancies [15]. In the analyzes performed, it was observed that there were great differences between the centers in the application of HIPEC treatment in colorectal cancer (Table 4) and questions about 1) method, 2) temperature degree, 3) volume of perfusate, 4) drug, 5) dose, 6) timing of drug use and 7) total perfusion time were asked by sending a form to all cancer centers in the US, which apply HIPEC treatment to provide a consensus between treatment practitioners. The response rate for the study was 69%, and 95% (n = 40) of the association members and respondents reported positive opinion for the standardization of operations in colorectal cancer. Based on the responses of participants to the study, the recommendations for the use of HIPEC treatment in colorectal cancer are summarized in the table below. The authors stated that there is a consensus on the standardization of HIPEC treatment in the USA, but further studies on this subject are needed.

Table 4: Comparison of HIPEC Treatment with CRS in Colorectal Cancer Patients[15]

Institution	Method	Drug	Dose	Timing	Temperature	Time (min)
USA						
Washington Hospital Center	Open	IP MMC IP Dox IV 5FU IV Leu	15mg/m^2 15mg/m^2 400mg/m^2 20mg/m^2 40mg	All at 0 minute 30 mg at 0 minute	41^{0}C 40^{0}C	90 120
Wake Forest University	Closed	MMC	40mg	30 mg at 0 minute	42^{0}C	90
St. Agnes Hospital	Closed	MMC	10mg at 45 minutes	2/3 at 0	41-42^{0}C	60
University California San Diego	Closed		10mg/L perfusate up to 60mg			
Germany						
Regensburg University	Closed	MMC Dox Oxali	20mg/m^2 15mg/m^2 300mg/m^2	All at 0 minute	41-42^{0}C	60
Spain						
MD Anderson Espana	Open	Oxali	460mg/m^2	All at 0 minute	43^{0}C	30
Sweden						
Uppsala University	Open	IP Oxali IV 5FU	460mg/m^2	All at 0 minute 1 hour before	41^{0}C	30
United Kingdom						
Basingstoke	Open	MMC	15mg/m^2	All at 0 minute	42^{0}C	60
Switzerland						
Kanton Hospital St Gallen	Open	MMC	25mg/m^2	1/3 every 30 minutes	42^{0}C	90

MMC: Mitomycin C, Dox: Doxorubicin, Leu: Leucovorin Oxal: Oxaliplatin, min: Minute

Table 5: HIPEC Standard of American Society of Peritoneal Surface Malignancies in Peritoneal Carcinomatosis Caused By Colorectal Cancer[15]

1	HIPEC Method	Closed
2	Drug	Mitomycin C
3	Dose	40 mg
4	Timing of Drug	30 mg at 0 minute, 10 mg at 60 minutes
5	Volume of Perfusate	3L
6	Temperature	42^{0}C
7	Duration of Perfusion	90 min

dk: Dakika

Choosing the right patient is the main indicator of success or failure of the treatment [16]. Studies have shown that various factors should be taken into account in the selection of patients in CRS + HIPEC treatment. Treatment is usually contraindicated in patients with high peritoneal tumor burden, additional peritoneal metastases, severe accompanying diseases and poor performance status [16]. One of the most important factors affecting the treatment is age and the operation is more effective in the group of patients with ≤60 years of age [9]. Although some centers have argued that this intervention is not appropriate for patients with >70 years of age, they have stated that age should not be the only factor per se for determining suitability to the treatment, and that decisions should be made according to individual case characteristics. A study supporting this opinion was made by Tabrizian et al. [17]. In the study, 170 patients who received HIPEC treatment with CRS due to the peritoneal carcinomatis, were divided into two groups according to their ages during operation: ≤65 (n = 35) and> 65 (n = 135). There is no difference between the two groups in terms of sex, peritoneal cancer index and accompanying diseases. The most common tumor sites in the study were colorectal and appendicular cancer. Complete cytoreduction (CCR 0-1) was achieved in 78.6% of the patients in the young group and in 82.4% of the patients in the elderly group. In the analyzes conducted, it is stated that as being above 65 years of age is not one of the variables explaining the morbidity, age should not be considered as a factor while making decision about the treatment. However, Razenberg et al. [16] found in their studies that treatment acceptance rates of young patients were higher than those between 60 and 70 years of age.

The level of peritoneal carcinomatosis is also an important factor as to determine for which patient the treatment will be administered. As indicated in some studies [18], intervention appears to be more effective in minimal and/or resectable peritoneal diseases. For example, in a study conducted by Jafari et al.[18], the median survival rate after CCR-0 surgery was 15 months, while the median survival rate was 4 months even after HIPEC treatment, in the case of macroscopic residues. According to the results of the study, the authors suggest that no HIPEC treatment should be performed in patients without a resectable peritoneal carcinomatosis.

Razenberg et al. [16] evaluated the developing trends in their study by examining the data set for the patients with colorectal cancer and peritoneal carcinomatosis (n = 4623) in the Netherlands, one of the countries in which HIPEC treatment with CRS

was first applied, between the years 2005 and 2012. 297 (6.4%) of these patients received HIPEC treatment combined with CRS. In the analyses, the use of this treatment method has been found to increase over years and it is revealed that 3.6% of the patients were treated with this method in 2005-2006, whereas this ratio increased to 9.7% in 2011-2012 ($p<0,0001$). It has been found that median overall survival was 32.3 months in patients received HIPEC treatment combined with CRS, while this ratio was 12.6 months for palliative chemotherapy with or without a surgical intervention, 6.1 months for palliative surgery and 1.5 months for best supportive care.

This technology is provided by a team of specially trained specialists in the tertiary health care-providing institutions. It has been emphasized that providing the training to the whole operating room team as the surgical method, chemotherapy perfusion, agents used and indications thereof and the results of the operation minimizes the risks [12]. In practice, the learning curve is of great importance, and the studies related thereto as well as their results are presented in the organizational aspects of the report.

It is seen that technology has been evaluated in Austria, the United Kingdom and Sweden when the reimbursement status of HIPEC treatment with CRS is taken into consideration. In the first evaluation in Austria it was proposed that the technology would not reimbursed and would be re-evaluated later, based on the results of Phase III studies [19].

In the United Kingdom, technology and available evidence indicate that treatment has provided some survival benefits in the treatment of colorectal metastases in the selected patients, but there is limited evidence for other types of cancer. Again, according to this assessment, technology should only be used in limited situations because of the high risk of technology mortality and morbidity [20].

According to the Swedish Center for Regional Health Technology Assessment, when HIPEC with CRS and systemic chemotherapy are compared in patients with colorectal cancer and peritoneal carcinomatosis, there is limited evidence for improvement in survival time and the effect of treatment on the quality of life is unknown. Prolongation of survival time is possible in particularly in patients with complete cytoreduction, which suggests that some criteria are needed for the patient selection. It was also noted in assessments that HIPEC treatment with CRS resulted in high morbidity, mortality and costs [21].

In Italy, the treatment is paid within Diagnosis Related Groups. In published studies it has been stated that treatment has no unique code and therefore the reimbursement is paid under other treatment groups, which does not reflect the actual costs, and the treatment therefore must have its own code. [22,23]. In the United States (USA) both private health insurance and Medicare and Medicaid reimbursed the treatment [24].

In Turkey, HIPEC with CRS has been reimbursed by the Social Security Institution (SSI) in tertiary health care institutions since 2012 within the scope of Annex-2B fee for service, and the transaction score was set at 1.773.09. Chemotherapeutic agents used during treatment can be invoiced separately.

In the treatment of peritoneal carcinomatosis, an alternative for HIPEC with CRS is CRS alone or systemic chemotherapy, and there is only a limited number of studies comparing both alternatives as discussed in the clinical effectiveness section. The limited number of randomized clinical trials and meta-analyzes in this treatment field causes drawback in both evaluating and using the technology. While the chemotherapeutic agents used in HIPEC treatment may be in different doses and combinations, whereas there is a limited number of studies related to their clinical effectiveness and safety. The results of the systematic literature review are summarized in the clinical effectiveness section of the report.

3.3. Discussion and Result

HIPEC therapy with CRS is a major medical intervention that requires specially trained personnel and equipment, which has been developed for the treatment of peritoneal carcinomatosis developed after a primary cancer. Although the treatment began to be developed from the beginning of the 1990s, there are no treatment guidelines on which a full consensus has been reached and standardization in the treatment has not yet been established. In some countries, including Turkey, although the treatment is within the scope of reimbursement of some reimbursement agencies, the technology assessment process is still in progress.

3.4. References

1- *Dubé P, Sideris L, Law C, et al. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms. Curr Oncol. 2015; 22:100-112.*

2- *Huang JY, Xu YY, Sun Z, et al. Comparison Different Methods of Intraoperative and Intraperitoneal Chemotherapy for Patients with Gastric Cancer: A Meta-analysis. Asian pacific j Cancer Prev. 2012;13(9):4379-4385.*

3- *Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. Cancer. 2012;12:526-536.*

4- *Topgul, K, Cetinkaya MB, N. Arslan NC, et al. Cytoreductive surgery (SRC) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal carcinomatosis: Our initial experience and technical details. Ulusal Cerrahi Derg. 2015;31:138-147.*

5- *Chua, TC, Martin S, Cert G, et al. Evaluation of the Cost-Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (Peritonectomy) at the St George Hospital Peritoneal Surface Malignancy Program. Ann Surg. 2010;251:323-329.*

6- *Verzijden JCM, Klaver YLB, de Hingh IHJT, et al. Cytoreductive surgery and hyperthermic intraperitoenal chemotherapy (HIPECI for peritoneal carsinomatosis in patients with colorectal cancer (Protocol). Cochrane Database of Systematic Reviews. 2010; Issue 4, Art No: CD008479.*

7- *Wu HT, Yang XJ, Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel to treat synchronous peritoneal carcinomatosis from gastric cancer: Results from a Chinese center. ESJO.2016; 42:1024-1034*

8-*Rodier, S, Saint-Lorant G, Guilloit JM, et al. Is hyperthermic intraperitoneal chemotherapy (HIPEC) safe for healthcare workers?. Surgical Oncology.2017; 26: 242-251.*

9- *Li Y, Zhou YF, Liang H, et al. Chinese expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies. World Jorunal of Gastroenterology. 2016;22(30): 6906-6916.*

10- *Jacquet P and Sugarbaker, PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res.1996; 82:359-374.*

11- *Terzi C, Yılmaz U, Yakut C, et al. Kolorektal kanser kaynaklı peritoneal karsinomatozis olgusunda sitoredüksiyon ve hipertermik intraperitoneal kemoterapi uygulaması ve literatürün gözden geçirilmesi. Ulusal Cerrahi Dergisi.2008; 24(1): 31-39.*

12- *Kyriazanos I, Kalles V, Stefanopoulos A, et al. Operating personnel safety during the administration of Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Surgical Oncology. 2016; 25:308-314.*

13- *Al-Quteimat, OM. and Al-Badaineh, MA. Intraperitoneal chemotherapy: Rationale, applications, and limitations. Journal of Oncology Pharmacy Practice. 2014;20(5): 369-380.*

14- *Braam HJ, Boerma D, Wiezer MJ, et al. Cytoreductive surgery and HIPEC in treatment of colorectal peritoneal carcinomatosis: experiment or standard care? A survey among oncologic surgeons and medical oncologists. Int. J. Clin.Oncol. 2015;20: 928-934.*

15- *Turaga K, Levine E, Barone R, et al. Consensus Guidelines from The American Society of Peritoneal Surface Malignancies on Standardizing the Delivery of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Colorectal Cancer Patients in the United States. Ann Surg Oncol.2014;21:1501-1505.*

16- *Razenberg LGEM., van Gestel YRBM, Creemers G-J et al. Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands. ESJO.2015; 41: 466-471.*

17- *Tabrizian P, Jibara G, Shrager, et al. Outcomes for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the elderly. Surgical Oncology. 2013;22:184-189.*

18- *Jafari MD, Halabi WJ, Stamos MJ, et al. Surgical Outcomes of Hyperthermic Intraperitoneal Chemotherapy Analysis of the American College of Surgeons National Surgical Quality Improvement Program.JAMA Surg.2014;149(2):170-175.*

19- *Ludwig Boltzmann Institut. Health Technology Assessment, Zytoreduktive Chirurgie und hypertherme intraperitoneale Chemotherapie bei Peritonealkarzinose. Decision Support Dokument Nr.: 74. 2014. Austria.*

20- *National Institute for Health and Care Excellence. Cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. 2010. United Kingdom.*

21- *Ludwigs K., et al. Cytoreduktiv kirurgi med intraperitoneal cytostatika (HIPEC eller EPIC) vid kolorektalt adenocarcinom och peritoneal carcinos. [Cytoreductive surgery and intraperitoneal chemotherapy (HIPEC or EPIC) in patients with colorectal adenocarcinoma and peritoneal carcinomatosis.] Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum.2013.HTA-rapport 57.*

22- *Bagnoli PF, Cananzi FCM, Brocchi A, et al. Peritonectomy and hyperthermic intraperitoneal chemotherapy: Cost analysis and sustainability. EJSO.2015; 41: 386-391.*

23- *Baratti D, Scivales A, Balestra MR, et al. Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). EJSO.2010;36:463-469.*

24- *Squires MH, Staley CA, Knechtle W, et al. Association Between Hospital Finances, Payer Mix, and Complications After Hyperthermic Intraperitoneal Chemotherapy: Deficiencies in the Current Healthcare Reimbursement System and Future Implications.Ann Surg Oncol.2015;22:1739-1745.*

4. Safety

4.1. Introduction

In this section, information on the safety of HIPEC will be presented within the scope of the findings obtained as a result of the systematic literature review. Answers to the questions contained in the section titled safety in HTA Core Model within the scope of the methodological approach further described in this section.

4.2. Assessments

HIPEC intervention with CRS in the treatment of peritoneal carcinomatosis is a major intervention and includes problems of both treatment related to the safety, as it includes both surgical and chemotherapeutic treatment. Therefore, when assessing safety-related data, it should be considered that the data of a major treatment, rather than any treatment, are being assessed. As can be seen from the study results below, some outcomes, which are not considered to be tolerable when assessing another treatment, should be accepted as in tolerable limits for this treatment. Two considerations need to be taken into account when assessing the safety of HIPEC treatment with CRS. First, as noted above, research on this treatment is usually a single-center, non-randomized studies performed on a limited number of patients. As the number of Phase III trials and randomized clinical trials in which the treatment is performed for all aspects and its comparative analyses are carried out is limited, then the number of meta-analyses is also limited. Secondly, it is necessary to evaluate the safety of treatment both in terms of receivers of the treatment and providers of the treatment. Although majority of the studies assesses the effect on the receivers of the treatment, some studies were performed with respect to how the providers of the treatment are affected. The following are the results of these studies:

Employee Safety

Kyriazanos et al. [1] list the precautions to be taken in order to provide safety regarding HIPEC treatment as follows:

> ***1. Preparation of operating room and operating room staff***
>
> Continuous and regular training should be given to the operating room team and training should be mandatory for everyone. Every new person added to the team should be given a detailed training. This staff should also be regularly checked through health check, pregnant staff should not participate in the procedures.

The chemotherapeutic solution should be prepared in a hospital pharmacy or elsewhere using a biological safety cabinet. The solution should be prepared in a non-leaking container with a suitable label. Guidelines on how to perform the chemotherapy should be hung in appropriate places in the operating room.

2. Protective equipment that must be used by the staff during HIPEC

All staff in the operating room should wear protective equipment that is compatible with the work they are doing. This equipment consists of masks, gloves, protective clothing and shoes. The simple surgical masks used for other surgeries are not suitable for these surgeries because they do not have the ability to retain particulates and vapors. It is necessary to use masks developed for this purpose. Surgical clothing should be waterproof, should prevent the drug from penetrating into the body and should be replaced immediately if there is minimal damage to clothing. The glove used should be the glove that will provide the best protection against the characteristic of the agent used in chemotherapy. It is recommended that double gloves should be worn and gloves should not be worn for longer than 30 minutes.

3. Chemotherapy application during HIPEC

All staff involved in the preparation of the chemotherapy solution should receive special training on this issue. System integrity should be checked with a non-toxic test solution before drug circulation. The use of a smoke evacuation system can help preventing airborne contamination. In the case of open HIPEC, a smoke evacuation should be used continuously under plastic cover during perfusion. Towels should be placed to absorb the agents that splash around the floor and the operating table.

4. Management of chemotherapy agent splashes

All precautions must be taken to prevent any splashing. Written policies and procedures regarding this should be determined and the whole operation team should be informed about it.

5. Management of waste after HIPEC

A clear policy for the management of waste containing chemotherapeutic agents should be established. The persons involved in this matter are principally the directors of the institution in which the process is carried out. Regulations on waste management may vary according to the rules of each country.

As stated above, safety issues in the treatment of HIPEC together with CRS should be evaluated for the receivers and providers of the treatment. A study examining the safety of the ones providing service was conducted by Rodier et al. [2]. According to the authors, HIPEC is one of the most risky interventions in terms of surgical teams. Exposure to antineoplastic medicines for health professionals is a major challenge. During HIPEC, health care providers are exposed to cytotoxic drugs in different ways in the operating room. The ones who are most exposed to these drugs in the team are surgeons. Rodier et al. [2] conducted a systematic literature analysis to analyze this aspect of HIPEC. As a result of the analysis, it was revealed that the first publication about the contamination risk of HIPEC was made in 2002, i.e. 20 years after the development of the treatment. The authors reached nine publications about the safety of HIPEC in terms of healthcare providers during the period examined. In the systematic literature review, only 55 HIPEC treatments were evaluated in this respect, and it was assessed that the antineoplastic agents used had the ability to penetrate into the organism, thus they are very dangerous. Furthermore, as observed from these studies, the materials used by the surgery teams to protect themselves from these materials vary widely, and there is no standardization in this sense. Environmental contamination was observed on all surfaces in the operating room. However, the authors emphasized that the effects of this treatment on healthcare providers could not be adequately assessed because of the lack of evaluation of biological samples in these studies and in the HIPEC procedures, and that studies on this subject and research on biological specimens should be increased.

Patient Safety

The incidence of grade III and IV adverse events in the studies related to patient safety in HIPEC treatment with CRS ranges from 11% to 30%. Adverse events differ according to PCI score, duration of operation, number of anastomoses, and the resected organ or peritoneum [3]. Common adverse events may include anastomotic leakage, bowel obstruction, renal failure, and bone marrow suppression. Postoperative mortality can vary between 0-11%. The most important causes of mortality are bowel leakage, bone marrow suppression, respiratory insufficiency, methicillin-resistant staphylococcus aureus and pulmonary embolism [3]. Researchers generally state that the conclusions reached when considering the extent of the disease and the treatment are tolerable. The results of these studies are summarized below.

- In a study conducted by Wu et al. [4] on 50 patients and 52 procedures, the objective of which is to demonstrate the clinical effectiveness and safety of HIPEC+CRS, in 12 (23.1%) of 52 procedures severe adverse events (grade III and IV) were developed. Adverse events seen were hypoalbuminemia (grade III, n = 4), postoperative bowel obstruction (grade 3, n = 3), septicemia (grade IV, n = 2), bowel leakage (grade IV, n = 1), diarrhea (grade III, n = 1), vomiting (grade III, n = 1). Four of the patients died within 90 days of the operation.
- In a multicenter study conducted on 401 patients by Yan et al. [5], the results of HIPEC treatment combined with CRS in the treatment of malignant peritoneal mesothelioma were evaluated. In the analyzes performed, 11% of the patients had respiratory complications, 18% had adverse events related to intestines, 10% had complications related to the kidney and 6% had hematologic toxicity. In general, 31% of the patients had grade III-IV adverse events and 2% of patients died.
- In an assessment performed by Jafari et al. [6] and carried out on 694 patients who were undergone operations at the centers affiliated to National Surgical Quality Improvement Program of American College of Surgeons, the most common adverse events were reported as follows: postoperative bleeding in 17% of patients, septic shock in 16%, pulmonary complications in 15% and organ infections in 9%. Similarly to the other studies, the overall mortality rate in the study was to be 2%.
- Desantis et al. [7] assessed the mortality and grade III and IV adverse events in 401 HIPEC procedures combined with CRS on 356 patients. Of the patients participating in the study, 49.4% had ovarian cancer, 20% had peritoneal carcinomatosis caused by colorectal cancer and the others had pseudo mycosis peritonei, peritoneal mesothelioma, gastric cancer and the like. As a result of analysis, the mortality rate was 1%, grade III and IV adverse event rate was found to be 12.5%. One of four deaths occurred from renal failure, one from bone marrow aplasia and one from multiple organ failure, and one from neoplastic pericardial effusion. The adverse events seen were listed as enteric fistula, intraabdominal abscess, pneumonia, small bowel obstruction, pancreatitis and neutropenia, and the length of hospital stay and recovery time of these patients were determined to be prolonged after these adverse events.

- Simkens et al. [8] have investigated one-year mortality rates, indicating that 30-day mortality rates do not reflect the accurate postoperative mortality risk because HIPEC treatment combined with CRS is a comprehensive treatment. A total of 245 patients treated at two tertiary health centers between April 2005 and April 2013, who underwent complete macroscopic reduction were included in the study. The causes of mortality were examined in these patients and the data of the patients who died and not died within 12 months were compared. 13,9% (34 patients) of patients participating in the study died within 12 months after CRS + HIPEC treatment. The overall mortality rate for the treatment was 4.9% (n = 12), 30-day mortality rate was 1.6% (n = 4) and the hospital mortality rate was 2.4% (n = 6). 7.3% (n = 18) of the patients died due to early recurrence. The overall survival of patients who were still alive one year after the operation was found to be 40 months. The table below presents the causes of mortality in the first year.

Table 6: Causes of 1-Year Mortality in HIPEC Treatment with CRS[8]

Cause of Death	N (%)	Details	N (%)
Treatment-related complications	12 (4,9)	Anastomotic Leakage Intraabdominal abscess and fistula Infected Urinoma	7 (2,9) 4 (1,6) 1 (0,4)
Early recurrence	18 (7,3)	Regional metastasis Systemic metastasis Both regional and systemic metastasis Unknown location	7 (2,9) 2 (0,8) 8 (3,3) 1 (0,4)
Known preoperative liver metastasis	1 (0,4)	Liver metastasis	1 (0,4)
Cardiovascular events	3 (1,2)	Cardiac arrest Abdominal aortic aneurysm rupture	2 (0,8) 1 (0,4)
Total	34 (13,9)		34 (13,9)

- In a retrospective study conducted by Bakrin et al. [9] on 607 operation data of 567 patients in France, the results of HIPEC treatment combined with CRS in the treatment of advanced epithelial ovarian cancer-induced peritoneal carcinomatosis were examined. Five of the patients participating in the study

died after surgery (0,8%). In the 31.3% (n = 190) of the procedures grade III and IV complications occurred. Intraabdominal hemorrhage was seen in 5% (n = 33) of the patients, whereas 11% (n = 69) had grade 3 or 4 leukopenia. Digestive fistula was seen in 3% of the patients (n = 16) and postoperative renal failure (2% chronic insufficiency, 1% long term dialysis) was seen in 8% (n = 51) of the patients. In multivariate analyzes, there was found a correlation between occurrence of adverse event and a peritoneal cancer index score of greater than 8 (Odds Ratio 2,17; p= 0,003), CC-1 and CC-2 (Odds Ratio 2,06; p =0,031) and use of cisplatin (Odds Ratio 3,08; p= 0,002).

- In a study conducted by Costa et al. [10] and aimed at evaluating the safety results of preoperative chemotherapy and HIPEC in patients with high-risk gastric cancer, outcomes of ten patients were evaluated. Patients participating in the study received three cycles of docetaxel (75mg/m^2), cisplatin (75mg/m^2) and intravenous 5-fluorouracil for five days before surgery and then received HIPEC treatment with mitomycin C (34mg / m^2). Postoperative morbidity was 50% and there were no case resulting in death.

- In a study conducted by Kusamura et al. [11], it was aimed to evaluate the mortality related to postoperative systemic toxicity and procedure in CRS and HIPEC treatment in peritoneal surface malignancies. 247 procedures performed on a total of 242 patients were examined. HIPEC technique was applied with cisplatin (CDDP 25 mg/m^2/l perfusate) +mitomycin C (MMC 3,3 mg/m^2/perfusate) or CDDP (43 mg/l perfusate) +doxorubicin (Dx 15,25 mg/l perfusate) at 42,5°C. If the patient had previously received systemic chemotherapy, these rates were reduced by 30%. According to the results of the study, systemic toxicity rates at grade III-V were 11.7% and adverse events were 13 bone marrow suppressions, 14 nephrotoxicities, 2 neutropenic infections and 1 pulmonary toxicity. The authors have concluded that the HIPEC treatment has an acceptable rate of systemic toxicity. The incidence of systemic toxicity in patients receiving CDDP+Dx was 2.36-times higher than in patients receiving CDDP+MCC. In the study, the mortality rate related to the operation was found to be 1.2%. Three of the patients participating in the study died in the days following the operation. The first death was due to duodenal perforation resulting from abdominal bleeding 21 days after surgery, the second death was due to microangiopathic hemolytic anemia syndrome, colic perforation,

bronchial haemorrhage and sepsis 26 days after surgery, and the third death was due to general sepsis and respiratory failure 27 days after surgery.

- In a study performed by Baratti et al. [12] to evaluate the safety of HIPEC combined with CRS as the primary endpoint, the procedures of 426 patients were examined. The correlation of the peritoneal cancer index, the number of visceral resections and the cisplatin dose higher than 240 mg with the morbidity was analyzed in the study. There was no correlation between the number and type of peritoneal peritonectomy and the type of visceral resection, and complications. The mortality rate in the study was found to be 2.6% (11/426) and the causes of death were multiple organ failure (due to bowel complications (8 patients) or abdominal abscess (1 patient)) in 9 patients, myocardial infarction in one patient and respiratory insufficiency one patient, respectively. In 34.5% (134 patients) of patients, recovery was achieved without adverse events, 23.9% (102 patients) had grade one, 16.6% (71 patients) had grade two, 11.7% (50 patients) had grade 3 and 13.6% (58 patients) had grade 4 adverse events. The most common adverse events were bowel complications due to anastomotic opening or intestinal rupture. In general, the rate of grade three and four adverse event development was 28.2%. The re-operation rate was found to be 10.7%. The authors concluded as a result of the study that the mortality and morbidity of HIPEC treatment combined with CRS were within acceptable limits.
- In a study conducted by Arslan et al. [13] at a center in Turkey, it was aimed to investigate factors related to infectious complications in patients with colorectal cancer-induced peritoneal carcinomatosis. In the study, HIPEC with CRS was administered to 50 patients in total and the infectious complication rate was found to be 34.6% (n = 18). The most common infectious complication was surgical site infection (n = 14) and 44% (n = 8) of them were classified as serious infectious complications. In the study, length of intensive care unit stay (odds ratio (OR): 2,113), preoperative albumin level (OR: 3,452) and duration of operation (OR: 1,986) were determined as independent prognostic factors associated with infectious complications.

Another safety assessment in the treatment of HIPEC with CRS was made in connection with the chemotherapeutic agent used in HIPEC. The studies on this subject are summarized below.

- Data of 100 patients and 105 procedures were evaluated by Wu et al. [14] to determine the effectiveness of the loboplatin and docetaxel use on survival in the treatment of HIPEC combined with CRS in abdominal and pelvic malignancies. Serious adverse events occurred in 15% (n = 16) of the patients participating in the study. Five of the patients had gastrointestinal obstruction, two had serious diarrhea (grade III), four had septicemia, and two had acute myocardial infarction. The authors stated that these results are acceptable results in terms of the safety of the treatment.
- In a study by Ceelen et al. [15], the safety of HIPEC treatment applied using high-dose oxaliplatin (460 mg / m^2) in patients with peritoneal carcinomatosis was evaluated. 52 patients participated in the study, with major morbidity being observed in 24% of patients and no 30-day mortality being seen. Chemoperfusion with oxaliplatin resulted in moderate hepatic toxicity one month after the operation, and after 14.5 months of follow-up, 9 patients died due to progression. The authors state that although studies in which patients' results should be monitored for longer periods of time should be done, high doses of oxaliplatin and CRS + HIPEC treatment had acceptable results in terms of morbidity, according to the results of this study.
- In a multicenter phase II clinical trial carried out by Hompes et al. [16] in Belgium, the effectiveness of HIPEC treatment with CRS and oxaliplatin in the treatment of colorectal cancer-induced peritoneal carcinomatosis was investigated. 48 patients were enrolled in the study and the overall complication rate was 52.1% and the 30-day mortality rate was 0. Anastomotic leakage was observed in 10.4% of patients, hemorrhage in 6.3% and prolonged ileus in 22.9%. 20,8% of the cases required re-surgical intervention. These results are consistent with other findings in the literature and the authors pointed out the importance of patient selection to reduce the complication rate.
- Votanopoulos et al. [17] examined the effect of mitomycin C or oxaliplatin use on haematological toxicity in patients with appendicular or colorectal-derived peritoneal carcinomatous in HIPEC treatment combined with CRS. The study was a single-center retrospective study and the data of 187 patients were examined. In 55% of the participants, oxaliplatin was used in HIPEC treatment, whereas in 132 patients mitomycin C was used. Splenectomy was

performed in 50.8% of the patients. When the hematological toxicity of the patients in this group were compared, there was a statistically significant difference in platelet incidence (p = 0.02) and neutrophil toxicity (p = 0.05). Accordingly, the incidence of grade III and grade IV hematological toxicity was higher in patients for whom oxaliplatin was used. However, there was no statistically significant difference in these data for patients without splenectomy. The authors concluded that when oxaliplatin-based HIPEC treatment and mitomycin-based treatment are compared at the end of the study, both treatments have caused similar white blood cell toxicity, but the mitomycin-based treatment has caused higher platelet and neutrophil toxicity.

In a limited number of studies, the effectiveness of the treatment was analyzed comparatively with the alternative treatment method. These studies are summarized in the following.

- In a study conducted by Simkens et al. [8] to compare HIPEC combined with CRS and traditional colon cancer surgery, it was concluded that the postoperative complications and mortality of patients in the first group were higher. In patients in this group the average age was lower but tumor characteristics were worse and the surgery was more extensive. Postoperative complications in the CRS + HIPEC group were seen in 69.8% of the patients and in 23.3% of the patients in the traditional surgery group (p<0,001). Serious complications were seen in 23.3% of CRS + HIPEC patients and this ratio was found to be 14.9% (p=0,16) in patients undergoing traditional surgery although this difference therebetween was not statistically significant. After prolonged surgery, ileus was seen in 34.9% of patients in CRS + HIPEC group and in 12.5% of patients in the other group (p<0,001). In addition, the patients in the CRS + HIPEC group stayed in the intensive care unit and hospital for a longer time than the ones in the other group. Patients in this group had a higher rate of rehospitalization than the patients who had undergone a traditional surgery (6,4% versus %20,9 p=0,004). According to these results, the authors concluded that the case mix should be carefully selected during the selection of patients to whom a CRS + HIPEC treatment would be applied.
- In a study conducted by Yang et al. [18], clinical effectiveness and safety of HIPEC combined with CRS on gastric cancer-induced peritoneal carcinomatosis

were evaluated with a Phase III study and patients were randomized to CRS (n = 34) or CRS + HIPEC group only (n = 34). Adverse events occurred in 9 of the patients participating in the study, of which 4 (11.7%) were only in the CRS group and 5 were in the CRS + HIPEC group (14.7%), but the difference was not statistically significant (p=0,839). Adverse events seen include infection and sepsis, respiratory failure, gastrointestinal bleeding, severe bone marrow suppression and bowel obstruction.

As previously stated, a limited number of meta-analyzes have been conducted among the limited number of randomized clinical trials. The results of the safety of HIPEC treatment with CRS obtained from these analyzes are summarized below.

- Sun et al. [19] evaluated the effectiveness of HIPEC in gastric cancer patients with serosal invasion and safety data of 1062 patients in a meta-analysis comprising the results of 10 randomized controlled studies performed by randomized clinical trials in that field. In these studies, adverse events seen in patients treated with HIPEC are listed as bone marrow suppression, anastomotic leakage, bowel fistula, adherent ileus and liver dysfunction. Bone marrow suppression was reported in five studies and in one study, this adverse event was seen in zero patients in the control group in HIPEC group, in another study, it was seen in one patient in two control groups in HIPEC group, and still in yet other study, it was seen in four patients in six control groups in HIPEC group. Relative Risk (RR) value was 1.68 (95% Confidence Interval (CI) 0.62-4.58; p=0.31) and there was no statistically significant difference between HIPEC and control group. Similarly, in adverse events such as anastomotic leakage, bowel fistula, adherent ileus and liver dysfunction there was no statistically significant difference between HIPEC group and control group.
- In another meta-analysis by Yan et al. [20] which aims to demonstrate the effectiveness and safety of HIPEC in the treatment of gastric cancer, it was concluded that the risk of intra-abdominal abscess (Relative Risk (RR)= 2,37, 95%CI 1,32-4,26; P= 0,003) and neutropenia risk (RR = 4.33; 95% CI= 1.49-12.61; p = 0.007) were higher in HIPEC treatment.
- In a meta-analysis study conducted by Mi et al. [21] which aims to demonstrate the effectiveness and safety of HIPEC treatment in patients with advanced gastric cancer, HIPEC found not to increase the incidence of adverse events

such as anastomotic leakage, ileus, bowel rupture, myelosuppression, gastrointestinal response and hypohepathy. In the analyzes, it was stated that the abdominal pain increased after HIPEC but this pain naturally disappeared over time.

- In a study conducted by Chua et al. [22], repeated CRS and HIPEC was compared to primary CRS and HIPEC treatment in recurrent peritoneal metastasis and the results of treatment were examined for safety. The demographic characteristics of patients who undergone primary CRS (n = 466) and patients who undergone repeated CRS (n = 79) are similar. More blood transfusion (p = 0.019) and albumin use (p = 0.013) were required in the primer CRS group. Mortality and major complication rates were similar (mortality = 1,2% versus 0% p = 0,600, major complication 41% versus 42%, p = 0,806). In the 545 procedures performed, six deaths occurred (1.1%) and all of the deaths occurred in the primary CRS group. Residual pneumothorax was more common in the CRS group than in the other group (4% versus 12%, p= 0,03). The adverse events are determined as follows: infection (p=0,798), bleeding (p=1,000), cardiac (p=0,804), pneumonia (p=1,000), pleural effusion (p=0,696), fistula (p=0,594), perforation (p=0,085), abdominal events (p=0,900), renal failure (p=0,129), pancreatic fistula (p=0,105), re-operation (p=0.388), pulmonary embolism (p=1.000). There is no difference between the two groups in terms of the incidence of major complications. Factors leading to major complications after CRS were found to be HIPEC treatment (p = 0.042) and the length of hospital stay (p = 0.024).

4.3. Discussion and Result

As seen in the clinical studies summarized above, the mortality and morbidity data on the safety of HIPEC treatment with CRS in peritoneal carcinomatosis has remained within the acceptable limits for such a major treatment. The procedure has a safety effect on both the receivers and providers of the treatment, and both aspects should be considered at the centers providing this treatment.

The incidence of grade III-IV adverse events in HIPEC treatment with CRS ranges from 11% to 30%. The most common adverse events were adverse events such as anastomotic leakage, bowel obstruction, renal failure, bone marrow suppression,

hematologic toxicity, pulmonary complications, septic shock, organ failure. It has been concluded that variables such as frequency of adverse events, age of the patients, the PCI score, etc., are important, thus selection of patient for the treatment is also important.

In some of the safety studies, the effect of chemotherapeutic agents used on safety was also assessed. However, as the number of these studies was limited and only a small number of patients were involved, assessment of the effect of these agents on safety was limited.

In this concept, the mortality rates of intervention are also within acceptable limits for an intervention. In conclusion, in the literature, HIPEC treatment with CRS considered as a safe treatment in peritoneal carcinomatosis treatment in the case that correct patient selection and appropriate application have been accomplished.

4.4. References

1- Kyriazanos I, Kalles V, Stefanopoulos A, et al. Operating personnel safety during the administration of Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Surgical Oncology. 2016;25:308-314.

2- Rodier S, Saint-Lorant G, Guilloit JM, et al. Is hyperthermic intraperitoneal chemotherapy (HIPEC) safe for healthcare workers?. Surgical Oncology. 2017;26:242-251.

3- Li Y, Zhou YF, Liang H, et al. Chinese expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies. World Journal of Gastroenterology. 2016;22(30):6906-6916.

4- Wu HT, Yang XJ, Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel to treat synchronous peritoneal carcinomatosis from gastric cancer: Results from a Chinese center. ESJO. 2016;42:1024-1034.

5- Yan TD, Black D, Sugarbaker PH, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience. Journal of Clinical Oncology. 2009; 27(26): 6237-6242.

6- Jafari MD, Halabi WJ, Stamos MJ, et al. Surgical Outcomes of Hyperthermic Intraperitoneal Chemotherapy Analysis of the American College of Surgeons National Surgical Quality Improvement Program. JAMA Surg. 2014;149(2): 170-175.

7- Desantis MD, Bernard JL, Casanova V, et al. Morbidity, mortality, and oncological outcomes of 401 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC). langenbecks Arch Surg. 2015;400: 37-48.

8- Simkens GA, van Oudheusden TR, Braam HJ, et al. Treatment-Related Mortality After Cytoreductive Surgery and HIPEC in Patients with Colorectal Peritoneal Carcinomatosis is Underestimated by Conventional Parameters. Annals of Surgical Oncology. 2016; 23:99-105.

9- Bakrin N, Bereder JM, Decullier E, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients. EJSO. 2013;39: 1435-1443.

10- Costa WL, Coimbra FJF, Ribeiro HSC, et al. Safety and preliminary results of perioperative chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) for high-risk gastric cancer patients. World Journal of Surgical Oncology. 2012;10: 95-101.

11- Kusamura S, Baratti D, Younan R, et al. Impact of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Systemic Toxicity. Annals of Surgical Oncology. 2007;14(9): 2550-2558.

12- Baratti D, Kusamura S, Mingrone E, et al. Identification of a Subgroup of Patients at Highest Risk for Complications After Surgical Cytoreduction and Hyperthermic Intraperitoneal

Chemotherapy. Ann Surg. 2012;256: 334-341.

13- Arslan NC, Sokmen S, Oguz VA, ve diğerleri. et al. Kolorektal Kanser Kökenli Peritoneal Karsinomatoz Tedavisinde Enfeksiyöz Komplikasyonlar ve Risk Faktörleri. Kolon & Rektum Hastalıkları Dergisi. 2015;25(4):122-130.

14- Wu HT, Yang XJ, Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel improves survival for patients with peritoneal carcinomatosis from abdominal and pelvic malignancies. World Journal of Surgical Oncology. 2016;14: 246-258.

15- Ceelen WP, Peeters M, Houtmeyers P, et al. Safety and Efficacy of Hyperthermic Intraperitoneal Chemoperfusion with High-Dose Oxaliplatin in Patients with Peritoneal Carcinomatosis. Annals of Surgical Oncology. 2007;15(2): 535-541.

16- Hompes D, D'Hoore A, Van Cutsem E, et al. The Treatment of Peritoneal Carcinomatosis of Colorectal Cancer with Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) with Oxaliplatin: A Belgian Multicentre Prospective Phase II Clinical Study. Ann Surg Oncol. 2012;19: 2186-2194.

17- Votanopoulos K, Ihemelandu C, Shen P, et al. A comparison of hematologic toxicity profiles after heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C. Journal of Surgical Research. 2013 179: 133-139.

18- Yang X-J, Huang C-Q, Suo T, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial. Ann Surg Oncol. 2011;18:1575-1581.

19- Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials.BMC Cancer. 2012;12:526-536.

20- Yan TD, Black D, Sugarbaker PH, et al. A Systematic Review and Meta-analysis of the Randomized Controlled Trials on Adjuvant Intraperitoneal Chemotherapy for Resectable Gastric Cancer. Annals of Surgical Oncology. 2007;14(10): 2702-2713.

21- Mi D-H, Li Z, Yang K-H, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: A systematic review and meta analysis of randomised controlled trials. International Journal of Hyperthermia. 2013;29(2):156-167.

22- Chua, TC, Quinn LE, Zhao J, et al. Iterative Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Recurrent Peritoneal Metastases. Journal of Surgical Oncology. 2013; 108: 81-88.

5. Clinical Effectiveness

5.1. Introduction

In this section, information on the clinical effectiveness of HIPEC will be presented in the light of the findings obtained as a result of systematic literature review. Within the scope of the methodological approach further described in the section, answers to the questions in the section titled clinical effectiveness in the STD Core Model were given.

5.2. Assessments

The most important problem related to the clinical effectiveness of HIPEC treatment with CRS in the treatment of peritoneal carcinomatosis is that these studies are usually single center, non-randomized studies and have been performed with a small number of patients. As emphasized by some authors, as the number of randomized clinical trials and consequently the number of meta-analysis are few, there are some problems both in evaluating the effectiveness of the treatment and in the practice and acceptance of the intervention by the doctors [1,2]. One of the most important criteria in evaluating the effectiveness of an intervention is the comparative analysis performed with the alternatives of this treatment. The lack of comprehensive prospective studies comparing HIPEC treatment in combination with CRS with systemic chemotherapy or traditional surgery also causes oncologists to approach this treatment with suspicion [3]. In this section, the effectiveness results of the clinical trials obtained in the systematic literature review are addressed.

Meta-Analyzes

As a result of the literature review, four meta-analyzes have been obtained [4,5,6,7].

In a study by Huang et al. [4], studies comparing the HIPEC treatment combined with CRS to the surgical intervention alone in gastric cancer patients, or comparing different regimes in HIPEC treatment were assessed via the meta-analysis. As a result of the systematic literature analysis and assessments, 15 randomized clinical trials of 1,713 patients were obtained, of which 10 were eligible for meta-analysis. As a result of the analyses, it was concluded that HIPEC (Hazard Ratio: 0,60, $p<0,01$), HIPEC plus postoperative intraperitoneal chemotherapy (Hazard Ratio: 0,47, $p <0,01$) and normothermic intraoperative intraperitoneal chemotherapy (Hazard Ratio: 0,70, $p<0,01$) were effective in prolonging overall survival. Additional analyzes showed that intraperitoneal chemotherapy reduced postoperative hepatic metastasis by 73%

(Odds Ratio = 0.27, 95% CI = 0.12-0.67, P <0.01).

In a systematic analysis study conducted by Mi et al. [5], it was aimed to demonstrate the effectiveness of HIPEC treatment in patients with respectable advanced gastric cancer. As a result of the systematic literature analysis conducted in the study, 16 randomized controlled studies were obtained and these studies contained data of 1,906 patients in total. In the analyses, it was possible to compare HIPEC treatment only with surgical treatment. When HIPEC treatment combined with the surgical treatment and the surgical intervention alone were compared, it was revealed that there were statistically significant improvements in favor of combined treatment in survival rates in the first, second, third, fifth and ninth years. According to the results obtained, the hazard ratio was 2.99 in the first year (95% CI 2.21-4.05; p<0,00001); the hazard ratio in the second year was 2.43 (95% CI 1,81 -3,26; p<0,00001); the hazard ratio in the third year was 2.63 (95% CI 2,17-3,20; p<0,00001); the hazard ratio for the fifth year was 2.49 (95% CI 1.97 -3,14; p<0,00001) and the hazard ratio for the ninth year was 2.14 (95% CI 1,38 -3,32; p=0,0007). In addition, when compared with only surgical intervention, the recurrence ratios of the combined treatment were significantly reduced. Accordingly, the recurrence ratio in the second year is 0.42 (95%CI 0,29- 0,61; p<0,00001); the recurrence rate in the third year was 0.35 (% 95 CI 0,24-0,51; p<0,00001) and the recurrence rate in the fifth year was 0.47 (95%CI.0,39-0,56; p<0,00001).

Sun et al. [6] evaluated the effectiveness of HIPEC in gastric cancer patients with serosal invasion by randomized clinical trials performed in this field. In the study, randomized clinical trials that divided patients into two groups; namely those who underwent gastrectomy due to advanced gastric cancer, and those treated with HIPEC with CRS and patients who underwent only CRS (control group) were included in the meta-analysis. In the analyzes, the HIPEC group was divided into two groups, with mitomycin C for one and 5_FU for another. As a result of the literature review, 10 randomized controlled studies have been obtained. A total of 1,062 patients were enrolled in these studies and divided into two groups as HIPEC group (n = 518) and control group (n = 544). The analysis showed that a very significant improvement was observed in the HIPEC group for survival compared to the control group [in the group using mitomycin (RR=0,75, 95% CI 0,65-0,86; p<0,00001); in the group using 5-FU (RR=0,69, 95%CI 0,52-0,90, p<0,00001; in total (RR=0,73, 95% CI 0,64-

0,83, p<0,00001). It has also been demonstrated that the recurrence rate in the HIPEC group was lower as compared to the control group (RR=0,45, 95% CI 0,28-0,72; p=0,001). The authors concluded that HIPEC treatment extended the overall survival in treatment of advanced gastric cancer and prevented peritoneal local recurrence.

In another meta-analysis by Yan et al.[7], the objective is to demonstrate the effectiveness and safety of HIPEC in the treatment of locally advanced resectable gastric cancer. Studies in which the gastric cancer patients who did and did not undergo HIPEC treatment were compared were included in meta-analysis and ten randomized clinical trials were included in the analysis. In the analyses included in the study, 1,648 patients were included and 873 of them were subjected to HIPEC treatment, 775 did not. Analysis revealed that there was a significant improvement in survival in patients treated with HIPEC (hazard ratio= 0,60; 95% CI 0,43-0,83: p=0,002). The authors stated that it is possible to determine the effect of HIPEC on overall survival, whereas it is not possible to determine its effect on recurrence, because of the study design. The authors concluded that there were no significant results during comparisons between the two treatments in current studies and therefore emphasized the need for a well-designed, multi-center, prospective randomized clinical trial.

All the meta-analyses, the brief summaries of which is summarized above, studies comparing the HIPEC treatment combined with CRS and CRS alone in gastric cancer-induced peritoneal carcinomatosis were added in analyses. In general, according to the results of the analysis, HIPEC together with CRS increased the overall survival and showed that this could be achieved with tolerable mortality and morbidity.

Colorectal and Gastric Cancers

In the systematic literature review, two studies comparing HIPEC treatment combined with CRS with CRS alone were reached [8,9].

Simkens et al. [8] compared the short-term outcomes of CRS + HIPEC treatment with traditional colon cancer surgery. In the study, 371 patients were operated and 43 (12%) of them were treated with CRS + HIPEC. These patients had worse tumor characteristics and the surgery was more extensive. In addition, these patients are younger than the patients who receive traditional treatment and are in better health status. However, the post-operative outcomes were worse. Patients in this group had more post-operative complications (in 23.3% of CRS + HIPEC patients and in 14.9%

of patients underwent traditional surgery). The basic reason for this is that the tumor characteristics are worse and the surgery is more comprehensive in these patients, as mentioned above. For this reason, the authors stated that when choosing CRS + HIPEC patients in colorectal surgery, the appropriate case mix should be determined and patients should be selected accordingly.

As mentioned above, a small number of Phase III trials were conducted in HIPEC treatment with CRS. In one of these studies, Yang et al. (2011)[9] assessed the clinical effectiveness and safety of HIPEC treatment combined with CRS in gastric cancer-induced peritoneal carcinomatosis patients and patients were randomized to only CRS (n = 34) or CRS + HIPEC group (n = 34). The basic demographic and clinical characteristics in both groups are similar. According to the results of the study, the median overall survival was 6.5 months (95% CI 4.8-8.2 months) in the CRS group, 11.0 months (95% CI, 10.0-11.09 months) in the CRS + HIPEC group, (p = 0.046), and the difference therebetween was statistically significant. In multivariate analyses, CRS + HIPEC, CC0-1, systemic chemotherapy of ≥6 cycles, and the absence of serious side effects are independent predictors of survival. Since the authors consider the morbidity profile of the treatment as acceptable, they have recommended the use of CRS + HIPEC treatment as a therapy improving survival.

The number of studies comparing HIPEC treatment combined with CRS to systemic therapy is also limited. In this systematic analysis, two studies were obtained [10,11]. A study was conducted by Alzahrani et al. [10] to determine the long-term consequences of HIPEC combined with CRS at a center in Australia. 827 peritonectomy procedures performed between 1996 and 2014 were included in the study and 220 of them were peritoneal adenomucinosis, 191 were appendicular cancer, 234 were colorectal cancer, 73 were peritoneal mesothelioma, and 109 were in the other category. The five-year survival rates were found to be 80% for peritoneal adenomucinosis and the five-year survival rate for peritoneal mucinous adenocarcinomas was 42%. The 5-year survival rate for those with a peritoneal cancer index of <10 is 60%, 57% for those with an index of 10-20 and 37% for those with an index of > 20. The difference therebetween is statistically significant (p=0,09). The 5-year survival rate for those with a peritoneal cancer index of between 0-5 is 59%, 15% for those with an index of 6-10, 7% for those with an index of 11-15, and 0% for those with an index of 15%, and the difference is statistically significant (p=0.000). The five-year survival

rates for those with malignant peritoneal mesothelioma and peritoneal cancer index of 0 are 100%, whereas this rate is 55% and 39% for the indices of 10-20 and >20, respectively. The differences therebetween are statistically significant (p=0,01). The authors concluded that the HIPEC treatment combined with CRS resulted in longer survival times as compared to systemic treatment alone.

In a study by Mirnezami et al. [11], in patients with colorectal peritoneal metastases, HIPEC treatment combined with CRS was compared to systemic chemotherapy alone. In the study, a literature analysis was conducted to find out the studies comparing both treatments, and four studies were reached, three of which were case-control and one of which was randomized controlled (CRS+HIPEC n= 187; Systemic Chemotherapy n= 155). In the analyses, when CRS+HIPEC treatment and systemic treatment were compared, the two-year survival (Odds Ratio 2.78, 95% CI 1.72-4.51, P = 0.001) and five-year survival rates (Odds Ratio 4,07; 95% CI 2,17-7,64; P = 0.001) were found to be better. Mortality rate ranged between 0% and 8%. The authors conclude that despite the limited heterogeneity of studies, CRS + HIPEC treatment has a more positive prognosis in terms of moderate and long-term survival as compared to systemic chemotherapy alone.

As explained in the first section, HIPEC treatment with CRS can be performed by open or closed surgical methods. An analysis comparing both methods in the literature analysis was carried out by Passot et al. [12]. In this study, they compared the results of laparoscopic and open surgical methods in HIPEC treatment combined with CRS in peritoneal surface malignancies. 8 patients with a peritoneal cancer index of less than 10 between January 2011 and November 2012, who underwent CRS + HIPEC treatment with a laparoscopic approach were included in the study and were matched to a cohort of 8 patients with the same characteristics, who had been treated in the past. In the analyses, the length of hospital stay was shorter in the laparoscopic intervention group (19 days versus 12 days) and the difference was statistically significant. The duration of median follow-up was 192 days (43-638 days) and no patients died during this period. Complication was seen in only one patient. The authors have stated that this approach is a non-aggressive and may be applied to patients whose disease severity is low.

In another study examining the effect of laparoscopic surgery in the HIPEC treatment combined with CRS, Facchianove et al. [13] conducted a systematic literature review

to investigate the clinical effectiveness of laparoscopic HIPEC treatment performed for neoadjuvant, adjuvant or palliative purposes. Laparoscopic access is a method that is used when there is no need for CRS or when a limited resection is required. During the investigation, eight studies consisting of 183 patients in total were obtained. The treatment was neoadjuvant for 5 of these patients, adjuvant for 102 of them and palliative for 76 of them. During laparoscopic procedure, 86 patients have peritoneal carcinomatosis. A comprehensive laparoscopic CRS was performed in 10 of these patients prior to laparoscopic HIPEC. 37 of patients have gastric cancer, 9 have breast cancer, 7 have peritoneal mesothelioma, 13 have ovarian cancer, 11 have colorectal cancer, 4 have pancreatic cancer, 3 have appendicular neoplasm, 1 have primary peritoneal carcinoma and 1 have melanoma. No deaths or serious side effects have been found in any of the studies. The authors noted that there is no data on the actual effectiveness of the intervention due to the small number of studies conducted on this field, so that routine implementation cannot be recommended, but further studies are needed in this regard.

In the systematic literature analysis, there are also single-center studies other than the meta-analyses and comparative analyses summarized above. In these studies, the number of patients is generally lower and there is no comparison with alternative treatments, and the effectiveness and safety of the treatment is generally evaluated. Below is a summary of the studies obtained in this context.

- Van Oudheusden et al. [14] conducted a study to evaluate the clinical effectiveness of HIPEC treatment and CRS in patients with colorectal cancer who underwent immediate surgical intervention for peritoneal carcinomatosis. 149 patients with colorectal cancer who were referred to two research centers and who had peritoneal carcinomatosis were included in the study. In 36 (24.2%) of these patients, peritoneal carcinomatosis was diagnosed during immediate surgical operation performed to relieve symptoms of primary tumor and CRS + HIPEC was applied. In the remaining 113 patients, the patients were electively diagnosed and treated. Median survival was calculated as 36.1 months in those receiving acute treatment and 32.1 months in those receiving elective treatment. The difference is not statistically significant (p=0,73). The authors stated that the CRS + HIPEC option should be considered in immediate surgery operations due to acute symptoms.

- A phase II study was conducted to demonstrate the effectiveness of HIPEC combined with CRS in patients with peritoneal carcinomatous disease caused by colorectal cancer in a center in China [15]. 60 patients who had been subjected to 63 CRS + HIPEC treatments and who subsequently received chemotherapy were included in the study. Peritoneal cancer indices of patients participating in the study were observed as ≤20% in 47% of patients and complete CRS (CC0-1) was performed in 53% of patients. Median overall survival was 16 months (95% CI, 12.2-19.8 months), one-year survival was 70.5%, two-year survival was 34.2%, three-year survival was 22% and five-year survival was 22%. Mortality was 0 at 30 days after surgery, grade III and IV adverse events were 30.2%. Univariate analyses showed that the overall survival peritoneal cancer indices was ≤20, CC0-1 and postoperative chemotherapy greater than six cycles were more effective. In multivariate analysis, only CC0-1 and chemotherapy of ≥6 cycles were found effective. The authors concluded that CRS + HIPEC treatment in selected patients in China could improve overall survival within acceptable safety limits. The fact that the results of the study are lower than in the researches carried out in other communities is attributed to the fact that colorectal cancer patients in China are 10 years younger than the West and that the disease is more aggressive in younger patients.

- The study by Kuijpers et al. [16] investigated the long-term consequences of SR and HIPEC treatment in Holland following the Dutch protocol. 960 patients participated in the study, of whom 660 (69%) had peritoneal carcinomatous retroperitoneal disease due to colorectal cancer with the diagnosis of pseudomycosis peritonei. Macroscopic complete cytoreduction was achieved as a result of 767 procedures (80%) in this disease. Median hospital stay was 16 months (range 0-166 days), median progression-free survival was 15 months (95% GA 13-17 months) for colorectal cancer patients, and 53 months (95% GA 40-66 months) for pseudomyxima peritoneal patients . Median overall survival was 33 months (95% CI, 28-38 months) for colorectal cancer patients and 130 months (95% CI 98-162 months) for pseudomyxima peritoneal disease. The three-year survival rate in colorectal cancer was 46% and the five-year survival rate was 31%, while the three-year survival rate in pseudomyxima peritoneal disease was 77% and the five-year survival rate was 65%. The authors stated that these results suggest that the Netherlands SR and HIPEC protocol is a safe

and overall survival-improving approach and that studies should be conducted to find chemotherapy that is better compatible with SR and HIPEC treatment, but this approach is the best treatment for survival until these studies.

- In a multicenter phase II clinical trial by Hompes et al. [17] in Belgium, the effectiveness of the HIPEC treatment with CRS and oxaliplatin for colorectal cancer-induced peritoneal carcinomatosis was investigated. 48 patients were enrolled in the study and the median peritoneal cancer index was 11 (range 1-22), median operative period was 460 minutes (range 125-840 minutes), and 30-day mortality rate was 0%. The median follow-up period was 22.7 months (range 3,2-55,7), one-year overall survival was 97.9% (95% CI 86.1-99.7), and two-year overall survival was 88.7% (95% CI 73,6-95,4). In the first year, disease-free survival was found to be 65.8% (95% CI 52.3-76.2) and 45.5% (95% CI, 34.3-55.9) in the second year. Median time until the recurrence is 19.8 months.
- In a study conducted by Hultman et al. [18], it was aimed to determine the effectiveness of CRS and HIPEC treatment after neoadjuvant systemic chemotherapy in 18 patients with peritoneal carcinomatosis due to gastric cancer. The patients firstly were given neoadjuvant treatment for three months, followed by CRS + HIPEC + EPIC. The whole treatment was applied to only eight of the patients and overall survival was found to be 14.3 months (range 6.1 – 34.3, 95% CI 6.6 – 20.3). In six patients, macroscopic radical surgery was performed and overall survival was calculated as 19.1 months in these patients (range 6.1 – 34.3,% 95 CI 6.9 – 27.1). Death within 90 days after surgery was 10% (one patient) and adverse event rate was 62.5% (between grade II-IV). The authors suggested that in patients with peritoneal carcinomatosis after gastric cancer, overall survival time cannot be prolonged unless the macroscopic radical surgery is performed, but that treatment-induced morbidity is very high, so this treatment is not recommended to become a routine treatment without a randomized controlled trial.
- In a study by Li et al. [19] it was aimed to evaluate the survival benefits of CRS and HIPEC treatment in gastric cancer patients. The study was a single-center study and included 128 patients who were treated between 1992 and 2002. Survival results in the study were obtained with resected and non-resected groups and only resected, and the groups which were resected and

received HIPEC treatment. As a result of the analyses, five-year survival rates are 5.5% in patients in the resected group and 0% in patients in the non-resected group. The difference was statistically significant (P<0,001). The multivariate analyses revealed that prognosis was significantly better in patients underwent surgical resection than in others. Median survival was higher in resected patients than in non-resected patients (11,8 months versus 6,0 months). The cumulative survival rate for patients resected in the same way and received with HIPEC was higher than that of resected patients only and the difference was statistically significant (p=0,025). HIPEC was shown to exhibit a better prognosis in gastric cancer patients with peritoneal metastasis by the multivariate analyses for the survival (Relative Risk=2,261, p= 0,012).

- Desantis et al. [20] assessed mortality and grade III and IV adverse events in 401 HIPEC procedures combined with CRS conducted on 356 patients. According to the oncologic results of the study, the factors affecting survival were histologic type of carcinomatosis (p <0,0001), Sugarbaker Peritoneal Cancer Index (p <0,0001), surgeon's experience (p = 0,004), recurrence status of carcinomatosis (p=0,0009), whether chemotherapy was applied prior to CRS (p=0,0002), the number of regions affected by peritoneal carcinomatosis ((p<0,0001), duration of surgery (p=0,001), perioperative blood transfusion (p=0.002), the number of peritonectomy (p=0,001), the number of anastomoses (p=0,01), and the quality of surgery (p<0,0001). The median overall disease-free survival was found to be 16.8 months, which was 89.4 months for pseudomyxoma peritonei and 8.1 months for gastric cancer (p<0,0001).
- In a study by Yan et al. [21], the results of HIPEC treatment combined with CRS were evaluated in malignant peritoneal mesothelioma. The assessment was multi-centered and included data from 405 patients. The age average of the patients participating in the study was 50 (standard deviation 14 years) and 79% of them had epithelial tumors. 92% of the patients received HIPEC treatment, 31% had grade 3-4 complications. As a result of analyses, it is found that the median overall survival was 53 months (1-235 months), the 3-year survival rate was 60% and the 5-year survival rate was 47%. In the univariate analyses, it was revealed that ag e(≤50, p=0003), gender (female p<0,001), epithelial subtype (p=0,006), absence of lymph node metastasis (p=0,008),

absence of extra-abdominal metastasis (p=0,013), peritoneal cancer index (≤20, p=0,002), CC0 or CC1 (p<0,001) and HIPEC treatment (p=0,049) were important factors affecting the prognosis. The authors have concluded that the HIPEC treatment combined with CRS is successful for prolonging the overall survival in this patient group.

- In the single-center CRS+HIPEC study of Wu et al. [22] conducted on 50 patients (52 operations) using lobaplatin and docetaxel, it was aimed to demonstrate the effect of the treatment on the overall survival and safety. The median follow-up time for the patients was 22.5 months. At the end of the study, the median overall survival was 14.3 months (95% CI, 7.6-21.0). The overall survival rates for the first, second and third year were 58.0%, 40.0% and 32.0%, respectively.
- In a study by Turrini et al. [23], the effect of HIPEC treatment combined with CRS on postoperative results in peritoneal carcinomatosis treatment was investigated. Sixty patients were included in the study. The mortality rate was found to be 0%, whereas the morbidity rate was found to be 33%. Median survival time was 39 months, one-year survival rate was 100%, 3-year survival rate was 51% and 5-year survival rate was 37%.
- Jafari et al. [3] criticized the fact that the studies for HIPEC treatment combined with CRS were performed at a single center and the number of patients was limited, and assessed 30-day mortality and morbidity during surgeries conducted at the centers of National Surgical Quality Improvement Program of American College of Surgeons. Of the 694 patients who participated in the study, 14% had appendicular cancer, 11% had primary peritoneal cancer and 8% had colorectal cancer. In the study, rehospitalization rate was 11%, reoperation rate was 10% and overall mortality rate was 2% within 30 days. With these results, the authors have reached the conclusion that acceptable mortality and morbidity rates were found in the operations performed in these centers.
- In a study by Esquivel et al. [2] that presented the results of the American Society of Peritoneal Surface Malignancies, it was stated that CRS + HIPEC treatment should not be administered in patients who are expected to have incomplete cytoreduction and median survival time of 8 months. The society stated that at least 30 months of median survival should be targeted in colorectal cancer patients with peritoneal carcinomatosis.

- In a study conducted by Chua et al. [24], repeated CRS and HIPEC treatment (n=79) was compared to primary CRS and HIPEC treatment (n= 466) in the recurrent peritoneal metastasis and the results of the treatment was evaluated for safety and survival. In the study, median survival was 48 months, and five-year survival rate was 34%. According to the type of cancer, the 3-year survival rates were found to be 0%, 74%, 80% and 72% for colorectal, appendicular pseudomyxoma, peritoneal mesothelioma and appendicitis cancer, respectively. The independent survival determinants were age ($p = 0.049$), the time between primary CRS and HIPEC, and repeated CRS and HIPEC ($p = 0.008$), small bowel resection ($p < 0.001$) and HIPEC ($p = 0.005$).
- Wu et al. [25] evaluated data of 100 patients and 105 procedures in order to determine the effectiveness of loboplatin and docetaxel use on survival in the treatment of HIPEC combined with CRS for abdominal and pelvic malignancies. The patients participating in the study were administered lobaplatin of 50 mg/m^2 and docetaxel of 60 mg/m^2 in 6.000 mL normal saline at 43 ± 0.5°C for 60 minutes. Six days after the procedure, vital data were evaluated. One week after the operation, all the blood tests returned to normal. In the study, median overall survival was 24.2 months (95% CI, 15.0-33.4 months), one-year survival rate was 77.5%; the three-year survival rate was 32.5% and the five-year survival rate was 19.8%. In the analyses, the cause of peritoneal carcinomatosis, peritoneal cancer index, completeness grade of CRS operation, number of cycles of adjuvant chemotherapy and serious adverse events were found to be the prognostic factors maximally affecting the overall survival. The authors have concluded that the CRS + HIPEC treatment along with lobaplatin and docetaxel is a treatment which has an acceptable safety and prolongs the life span of the patients.
- In a study by Graziosi et al. [26] it was aimed to determine the prognostic factors for survival in the HIPEC treatment combined with CRS. The study was single-centered and included 64 patients. The five-year overall survival was found to be 55%. The location of primary tumor, the overall survival differed according to preoperative serum albumin levels, and the five-year survival was 70% in patients with high levels of serum albumin and was 38% ($p<0,05$) in patients whose levels were low. Another factor that affects

survival time is adverse events. Accordingly, three-year survival was 62% in patients with minor adverse events (grade I and II), whereas this ratio was 28% in patients with major adverse events ($p<0,01$). The authors have stated that CRS + HIPEC treatment in locally advanced gastrointestinal malignancies is an effective and reliable treatment if the preoperative parameters are well evaluated.

- Vassos et al. [27] analyzed data of 85 patients to evaluate the effectiveness of HIPEC treatment combined with CRS in patients with recurrent peritoneal carcinomatosis. Six (7%) of the patients participating in the study received a second CRS + HIPEC treatment, and two of them had mesothelioma, one had ovarian adenocarcinoma, one had uterine leiomyosarcoma, one had colon adenocarcinoma and one had appendicular adenocarcinoma. The median time between two procedures was 26 months (range 8-61). Patients with colon and appendicular carcinoma also had third operation after the second (median time was 14 months). The cytoreduction score of CC-0 was reached in all of the first operations and in 67% of the second operations. CC-0 score was reached in both of the third operations. After 30 days of repeated CRS + HIPEC, morbidity was 33% (16% grade III and IV) and mortality was seen neither 30 days after the second operation nor after the third operation. The disease-free survival time between first CRS + HIPEC and peritoneal recurrence was 17 months (range 8-30) and disease-free survival of 18 months (4-33) was provided after second operation. After a median follow-up of 74 months (range 39-151), all patients lived with disease (n = 5) or without disease (n = 1) under chemotherapy. The authors have noted that CRS + HIPEC treatment repeated at the experienced centers may be safely applied and the repeated CRS + HIPEC treatment may be considered a treatment option for the recurrent peritoneal carcinomatosis in the selected patients.

As can be seen, different results have been obtained in the studies on the clinical effectiveness of HIPEC treatment with CRS. The results of these studies for colorectal cancer-induced peritoneal carcinomatosis are summarized in Table 7, the results for gastric peritoneal carcinomatosis are summarized in Table 8, and the results for peritoneal mesothelioma-induced peritoneal carcinomatosis are summarized in Table 9 [19].

Table 7: Results of Phase II Trials of HIPEC Treatment with CRS in the Treatment of Colorectal Peritoneal Carcinomatosis[19]

Reference	Year	Patients	Mean Follow-Up (ay)	Overall Survival By Years (%)				
				1	2	3	4	5
Schneebaum et al.	1996	15	15	-	-	-	-	-
Elias et al.	1997	29	12	88	55	40	-	-
Pujimura et al.	1999	14	-	51	-	21	-	-
Loggie et al.	2000	36	27	60	39	24	-	-
Cavaliere et al.	2000	14	30	-	64	-	-	-
Witcamp et al.	2000	29	36	82	45	23	-	-
Beujard et al.	2000	21	12	50	-	-	-	-
Piso et al.	2000	17	39	-	-	-	75	-
Elias et al.	2001	64	36	60	47	36	-	27
Culliford et al.	2001	47	17	-	-	-	-	28
Zoetmulder et al.	2002	36	-	-	-	-	-	20
Shen et al.	2003	40	52	60	-	24	-	-
Pilati et al.	2003	34	14	-	31	-	-	-
Pestieau et al.	2003	99	-	100	-	-	-	30
Glehen et al.	2004	53	-	55	-	-	-	11
Toplam		**543**	**10-52**	**-**	**>40**	**-**	**-**	**20**

Table 8: Results of Clinic Trials of HIPEC Treatment with CRS in the Treatment of Gastric Peritoneal Carcinomatosis[19]

Reference	Patient	HIPEC	Morb. N(%)	Mort. N(%)	Median Follow-Up (month)	Median Survival (month)	Overall Survival		
							1	2	5
Yonemura et al.		Open technique MMC, 30mg, DDP 300mg, Etoposide 150mg, 8L normal saline, 42-43^{0}C, 60min	23 (15,9)	5 (2,8)	46	11,5 CCR0:19,2 CCR1-3:7,8	35,5	13,1	6,7
Yonemura et al.		Open technique, MMC 30mg,DDP 300mg, etoposide 150mg, 8L normal saline, 42-43^{o}C, 60 min	-	-	46	CCR 0: 13,9 CCR1-3: 6,8	45	-	11
Yonemura et al.		Open technique, MMC 30mg, DDP 300mg, 8L normal saline, 42-43^{0}C, 60 min.	9 (19,0)	2 (4,0)	-	-	-	-	61,0
Scaringi et al.		Closed technique, MMC 120mg, DDP 200mg, 6L normal saline, 42-43^{0}C, 90-120 min	10(38,5)	1 (3,8)	-	6,6	-	-	-
Fujimoto et al.		Closed technique, MMC 30-50 mg, 44,7-48,7^{0}C, 120 min	2 (13,3)	0	-	7,2±4,6	-	-	-
Fujimoto et al.		Closed technique, MMC 10mg/mL, 44,5-45^{0}C, 120 min	2 (2,8)	0	7	-	88,0	76,0	2,0
Hall vd		Closed technique, MMC 10mg/mL, 40^{0}C, 120 min	12 (35,0)	0	-	8	27,0	23,0	6,0

Devamı

Fujimura et al.		Open technique, MMC 20 mg/m^2, DDP 200mg/m^2, 6L normal saline, 42-52^{0}C, 90-120dk	6(19,4)	0	-	9	33,3	8,3	0,0
Hamazoe et al.		Closed technique, MMC 10ug/mL, inside 40-45^{0}C, outside 40-42^{0}C, 60 min	2 (4,8)	0	>6	77	90,0	80,0	64,3
Kim et al.		Closed technique, MMC 10ug/mL, inside 44^{0}C	19(36,5)	0	38	36	-	-	32,7
Yang et al.		Open technique, MMC 30mg, DDP 120 mg, 42^{0}C, 120 min	5 (14,7)	0	32	PCI≤20			
Chen et al.		Open technique, chlorhexidine diacetate hydrate 0,6, 4L water, 43^{0}C 4 min	-	-	-	-	88,7	66,2	63,6
Zhu et al.		Open technique, DDP 50mg/L, MMC 5mg/L, 43^{0}C, 60 min	-	-	72	-	76,9	69,2	55,2

Morb: Morbidity, Mort: Mortality, min: Minutes

Table 9: Results of Clinical Trials of HIPEC Treatment with CRS in the Treatment of

Gastric Peritoneal Carcinomatosis[19]

Reference	Patient	Country	Median Follow-Up (month)	Median OS (ay)	Median DSF (ay)	Morbidity (%)	Mortality (%)
Baratti et al.	12	Italy	27	-	24	-	0
Baratti et al.	12	Italy	64	-	11	8,3	0
Blackham vd.	34	USA	72	40,8	9,1	-	-
Brigand et al.	15	France	46,7	35,6	-	-	0
Chua et al.	20	Australia	18,1	29,5	7,2	65,0	5,0
Sebbag et al.	33	USA	21,3	31	-	33,0	3,0
Tudor et al.	20	Australia	18	30	8	65,0	5,0
Deraco et al.	61	Italy	20	-	28	23,0	0
Deraco et al.	116	Italy	-	31,4	14,4	41,3	2,6
Loggie et al.	12	USA	45,2	34,2	-	33,0	8
Ma et al.	12	Turkey	10	-	-	90,0	20
Macuks et al.	12	Turkey	-	-	-	-	-
Markman et al.	19	USA	25	19	-	-	-
Feldman et al.	49	USA	-	92	17	25,0	-
Chua et al.	26	Australia, Italy, France, USA	54	-	-	26,9	0
Schaub et al.	104	USA	49,4	52	20,8	-	-
Yan et al.	401	Australia, France, Italy, USA, UK, Germany	33	53	-	46,0	2
Yano et al.	17	UK	13	-	-	41,0	12
Yonemura et al.	21	Japan	-	-	-	46,2	-
Elias vd.	26	France	54	>100	40	54,0	4

OS: Overall Survival, DFS: Disease-Free Survival, USA: United states of America, et al: et alii, UK: United Kingdom

There is also a limited number of studies evaluating the treatment results in terms of quality of life in HIPEC treatment combined with CRS.[28,29,30]

- In a study conducted by Shan et al. [28], a systematic review and a meta-analysis were performed about the effect of HIPEC treatment combined with CRS on the health-related quality of life in peritoneal carcinomatosis. After the systematic analysis, 15 articles were reached and the total number of patients participating in these studies was 1.583. The analyses revealed that the health-related quality of life declined within 3-4 months and reached a level comparable to or better than the preoperative level after a year. Physical well-being decreases after surgical intervention and reaches its worst condition around the third month, but after 6 to 12 months it returns to its baseline level or reaches a better condition. On the other hand, social well-being does not show a significant change from the baseline level. Functional well-being returns to the preoperative level or reaches a better situation after 6-12 months, as is in the physical well-being. The greatest improvement is provided in the emotional well-being, and although it initially decreases due to surgery-related morbidity, it reached preoperative level or a better level within three months. Analyses showed that the recovery rate is 38%. The authors have concluded that, at the end of the study, HIPEC combined with CRS provided a noticeable benefit to the health-related quality of life of the patients and reached to a better or similar level than the preoperative level one or two years after the operation. The quantitative analyses showed an improvement of 28% compared to baseline.
- Tan et al. [29] examined the effect of HIPEC treatment combined with CRS on the quality of life in Asia population. 27 patients participated in the study and their quality of life was assessed by the European Organization for Research and Treatment of Cancer and Treatment of Cancer QlQ-C30 questionnaire. The results were compared with the scores of 393 cancer patients, the disease of whom was treated, who were not actively treated, and whose ECOG score was 0 or 1. Of the patients participating in the study, 55% (n = 15) had ovarian cancer, 19% (n = 5) had appendicular cancer; 15% (n = 4) had colorectal cancer. The median peritoneal cancer index score of the patients was 15, the CC score of 25 patients was 0, and the CC score of 2 patients was 1. The results of the

study showed that the scores of the control group and the patients who received CRS + HIPEC treatment were similar to each other (Table 10). As seen in the table, the authors have concluded that as a result of the study, the quality of life of the patients being treated was equivalent to the treated cancer patients.

Table 10: Comparison of Quality of Life Scores of the Patients Received HIPEC with CRS to the Scores of Cancer Patients without Disease [29]

Parameter for Quality of Life	Average Score (95% CI)	Reference Value	p value
Score of Function			
General Health	67 (59-75)	71	0,335
Physical Function	85 (78-91)	85	0,908
Role Function	89 (83-96)	87	0,487
Emotional Function	83 (76-89)	81	0,567
Cognitive Function	88 (83-94)	81	0,014*
Social Function	83 (74-93)	86	0,567
Score of Symptoms			
Weakness	17 (10-25)	25	0,040*
Nausea and Vomiting	7 (1-13)	4	0,308
Pain	13 (5-21)	18	0,204
Dyspnea	8 (2-15)	15	0,051
Sleeplessness	16 (6-25)	24	0,052
Lack of appetite	7 (1-14)	11	0,230
Constipation	12 (4-20)	11	0,820
Diarrhea	7 (1-14)	6	0,720
Financial Difficulty	21 (10-33)	23	0,776

** Statistically significant*

- In a study conducted by Tsilimparis et al. [30], the question of whether it is worth taking the risk of HIPEC treatment combined with CRS was asked and the effects of the treatment on the quality of life were examined. The study included 90 patients to whom the treatment was applied and the quality of life was measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. The results of the analyzes showed that the physical and role functions started to heal 6 months after surgery and reached baseline values at 24th month, emotional functions started at a low starting point and reached baseline values at 12th month, cognitive and social function proceeded slowly, fatigue, diarrhea, dyspnea and sleep disorders have remained stable during the 6-month follow-up period and improved in those

who lived. The authors have concluded that the aspects for the quality of life developed over time and therefore, the aspects for the quality of life should not be taken into account when assessing whether patients are accepted for the treatment. The results obtained from the study are presented in the table below.

Table 11: Average Function Scores During Hospital Visits After CRS and HIPEC Treatment[30]

Visit	General		Physical Function		Role Function		Emotional Function		Cognitive Function		Social Function	
	Avr	SD	Avr	SD	Avr	SD	Avr	SD	Avr	SD	Avr	SD
Reference	70,8	22,1	90,1	16,7	88,0	22,9	78,7	21,0	91,2	17,0	91,0	19,4
Baseline	69,3	24,7	85,5	20,7	77,5	28,4	63,7	26,8	90,6	16,4	69,3	28,5
1 month	54,9	20,3	57,9	23,9	46,2	31,3	54,9	21,6	74,5	27,7	44,9	28,9
6 months	66,3	22,2	71,6	22,7	59,1	29,3	62,7	22,3	74,6	24,8	55,9	27,0
12 months	66,4	23,6	75,6	23,7	58,9	34,4	60,9	26,1	78,1	23,7	59,4	32,8
24 months	70,6	22,8	75,3	23,4	74,5	29,5	66,7	27,0	80,4	22,2	66,7	32,8
36 months	77,8	20,8	86,7	11,2	72,2	25,1	76,4	17,8	86,1	16,4	69,4	24,5

Avr: Average, SD: Standard Deviation

Ovarian Cancers

In the systematic review of the literature, overcancer studies have been found in addition to gastric and colorectal cancer studies summarized above. In these studies, the number of patients is generally lower and there is no comparison with alternative treatments, and the efficacy and safety of the treatment is generally evaluated. Below is a summary of the work that occurs in this framework.

- In a retrospective study conducted by Bakrin et al. [31] on 607 procedure data of 567 patients in France, the results of HIPEC treatment combined with CRS were examined in the treatment of advanced epithelial ovarian cancer-induced peritoneal carcinomatosis. In the study, mortality rate was found to be 0.8%, whereas grade III and IV morbidity rates were 31.3%. Median overall survival was 35.4 months for advanced epithelial ovarian cancer and 45.7 months for recurrent epithelial ovarian cancer. The peritoneal cancer index and the extent of the disease were found to be the most important independent

variables determining the prognosis. One-year survival rate was 83%, three-year survival rate was 47% and five-year survival rate was 17%. The survival rates without recurrence were 52% in the first year, 18% in the third year and 12% in the fifth year. For patients treated with CC-0, the median survival was 41.5 months.

- Rettenmaier et al. [32] conducted a study consisting of 37 patients to demonstrate the effectiveness of the chemotherapy after laparoscopic CRS + HIPEC in the treatment of ovarian cancer. Patients participating in the study received chemotherapy regimens consisting of carboplatin and paclitaxel after surgery. Patients participating in the study were well tolerated to the treatment, there was no rehospitalization, and grade 3/4 anemia was observed in 6 patients. In the study, the disease-free survival was 13 months and the overall survival was 14 months. The authors concluded that this treatment was an appropriate and tolerable treatment, but they stated that additional studies were needed because of the fact that HIPEC is still a controversial treatment and the number of studies is limited.
- In a study by Giorgio et al. [33] the clinical effectiveness of the HIPEC treatment combined with CRS in the treatment of peritoneal carcinomatosis caused by ovarian cancer was evaluated. The study was a single-center, non-randomized Phase II trial and included 47 patients who had primary advanced or recurrent cancer. In the vast majority of patients participating in the study, satisfactory cytoreduction (CC-0/CC1) was achieved in 87.2% of the patients with intensive ovarian carcinomatosis (Peritoneal Cancer Index = 14,9), and complete cytoreduction (59.6%) was achieved in 59%. The mean survival time was found to be 30.4 months. The overall 5-year survival rate was found to be 16.7% when long-term results were considered. These results were considered to be consistent with the rates obtained in similar studies. The authors have concluded that HIPEC treatment combined with CRS is a promising method in terms of long-term survival for the patients with peritoneal ovarian carsomatosis and mortality and morbidity results thereof are acceptable.
- In a study conducted by Deraco et al. [34], the clinical effectiveness of HIPEC combined with secondary CRS in the recurrent epithelial ovarian cancer was examined. The study was a multicenter study consisting of 56 patients and 57

procedures. Cisplatin and doxorubicin, or cisplatin and mitomycin C were used in the HIPEC treatment. Median overall survival in the study was 25.7 months (95% CI 20.3-31.0) and progression-free survival was 10.8 months (95% CI 5.4-16.2). Five-year overall survival was 23% and five-year progression-free survival was 7%. The authors have stated that the HIPEC treatment combined with CRS is a promising treatment method in the treatment of recurrent epithelial ovarian cancer and that this method could provide long-term survival in patients with optimal ECOG status, preoperative albumin level of > 35 mg/dL and optimally cytoreductive disease.

- In another study by Ansaloloni et al. [35], the mortality and morbidity results of HIPEC treatment combined with CRS were evaluated in patients with peritoneal carcinomatosis caused by advanced epithelial ovarian cancer. The study is an open, prospective, non-randomized and one-centered phase II study. 39 patients were enrolled in the study and the age average was 57.3. In the study, no death was observed after surgery, and in 18% of the patients postoperative complications were developed. The operation was repeated for 8% of the patients and recurrence was observed in 59% of them. The average recurrence time was 14.4 months. The authors have concluded according to the results that HIPEC treatment combined with CRS is an appropriate treatment method in patients with peritoneal carcinomatosis caused by advanced epithelial ovarian cancer, but there is a need for additional studies.
- In Phase II study by Spiliotis et al. [36], 120 female patients with advanced stage overcancer (International Obstetrics and Gynecology [III] and IV) 120 were randomly assigned to HIPEC and systemic chemotherapy or cytoreductive surgery (SC) and systemic chemotherapy groups in 8 years (2006-2013) and the results evaluated. Mean survival in the HIPEC group was 26.7, whereas it was 13.4 months in the SC group ($p < 0.006$). Three-year life span was 75% for HIPEC and 18% for SC ($p < 0.01$). Mean survival in the HIPEC group was reported to be no different from platinum-sensitive disease versus platinum-sensitive disease (26.6 versus 26.8 months). It has been reported that full cytoreduction is effective for survival and patients with a peritoneal cancer index score <15 show longer survival.

5.3. Discussion and Result

A limited number of randomized clinical trials performed for evaluating clinical effectiveness of the HIPEC treatment with CRS in the treatment of peritoneal carcinomatosis demonstrate that this intervention improves the overall survival rates, survival rates in the first, second, third, fourth and fifth years, disease-free survival, and recurrence rates with correct patient selection. Analyses suggest that patient characteristics such as PCI (≤20), CC0-1 level, type of cancer causing peritoneal carcinomatosis, and age are effective in determining the results of the intervention. For this reason, case mix of the patients who will receive the intervention is important. However, problems arise while comparing the results, especially because of the methodology of single center and non-randomized trials, the characteristics of the patients, and the undetermined standards of the intervention. Thus, it is indicated in the literature that well-designed, multicenter, prospective, randomized clinical trials are required.

Only one randomized phase III study was reached in evaluating the clinical efficacy of HIPEC treatment in peritoneal carcinomatous cases depending on over cancer. The results of the Phase III study are quite promising. However, the lack of clarity of randomization and patient selection limits the evaluation of the data provided by the study. Although single-centered and non-randomized results are promising also. However, problems arise in comparing the results of the studies because of the methodology of the studies, the characteristics of the patients, and the standards of the intervention were not determined clearly. It is understood that a well-designed, multicenter, prospective, randomized clinical trials focusing on ovarian cancers are necessary, especially it is not possible the results of in the treatment of gastric and colon cancers for the interpretation of the outcome of HIPEC in the treatment of ovarian cancers.

There is small number of studies which examines the effect of HIPEC with CRS on quality of life. In these studies, it has been found that the intervention improves the quality of life and physical and mental aspects of the quality of life, which are at low levels before the intervention, reached the baseline level or a better level after 6-12 months.

Studies in the literature have evaluated survival and quality of life, but it has been observed that difficulties and anxieties have not been evaluated in terms of patients. It can be said that it is necessary from the point of view of patient centered health technology evaluation that new analysis are needed to understand patients suffering from medical treatment and post-procedural problems exposed to stress.

Briefly, an analysis of studies examining the clinical effectiveness of HIPEC treatment with CRS in peritoneal carcinomatosis reveals that the intervention has a positive effect on both overall survival and quality of life with accurate patient selection.

5.4. References

1- *Dubé P, Sideris L, Law C, et al. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms. Curr Oncol. 2015; 22:100-112.*

2- *Esquivel J, Piso P, Verwaal V, et al. American Society of Peritoneal Surface Malignancies Opinion Statement on Defining Expectations from Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Patients with Colorectal Cancer. Journal of Surgical Oncology. 2014;110: 777-778.*

3- *Jafari MD, Halabi WJ, Stamos MJ, et al. Surgical Outcomes of Hyperthermic Intraperitoneal Chemotherapy Analysis of the American College of Surgeons National Surgical Quality Improvement Program. JAMA Surg. 2014;149(2): 170-175.*

4- *Huang JY, Xu YY, Sun Z, et al. Comparison Different Methods of Intraoperative and Intraperitoneal Chemotherapy for Patients with Gastric Cancer: A Meta-analysis. Asian Pasific J Cancer Prev. 2012;13(9): 4379-4385.*

5- *Mi D-H, Li Z, Yang K-H, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: A systematic review and meta analysis of randomised controlled trials. International Journal of Hyperthermia. 2013;29(2): 156-167.*

6- *Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer. 2012;12:526-536.*

7- *Yan TD, Black D, Sugarbaker PH, et al. A Systematic Review and Meta-analysis of the Randomized Controlled Trials on Adjuvant Intraperitoneal Chemotherapy for Resectable Gastric Cancer. Annals of Surgical Oncology. 2007;14(10): 2702-2713.*

8- *Simkens GA, Verwaal VJ, Lemmens VE, et al. Short-term outcome in patients treated with cytoreduction and HIPEC compared to conventional colon cancer surgery. Medicine. 2016; 95: 41-48.*

9- *Yang X-J, Huang C-Q, Suo T, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial. Ann Surg Oncol. 2011;18: 1575-1581.*

10- *Alzahrani N, Ferguson JS, Valle SJ, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: long-term results at St George Hospital, Australia. Surgical Oncology.2015;86: 937-941.*

11- *Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with*

colorectal peritoneal metastases compared with systemic chemotherapy alone. British Journal of Cancer. 2014; 111: 1500-1508.

12- Passot G, Bakrin N, Isaac S, et al. Postoperative outcomes of laparoscopic vs open cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of peritoneal surface malignancies. Eur J Surg Oncol. 2014;40(8):957-62.

13- Facchiano E, Risio D, Kianmanesh R, et al. Laparoscopic Hyperthermic Intraperitoneal Chemotherapy: Indications, Aims, and Results: A Systematic Review of the Literature. Surg Oncol. 2012;19:2946-2950.

14- Van Oudheusden TR, Braam HJ, Nienhuijs SW, et al. Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy: A Feasible and Effective Option for Colorectal Cancer Patients After Emergency Surgery in the Presence of Peritoneal Carcinomatosis. Ann. Surg. Oncol. 2014;21:2621-2626.

15- Huang C-Q, Yang X-J, Yu Y, et al. Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival for Patients with Peritoneal Carcinomatosis from Colorectal Cancer: A Phase II Study from a Chinese Center. PLoS One. 2014 Sep 26;9(9):e108509

16- Kuijpers AM, Hauptmann M, Aalbers AG, et al. Cytoreduction and HIPEC in The Netherlands: Nationwide Long-term Outcome Following the Dutch Protocol. Ann Surg Oncol. 2013;20: 4224-4230.

17- Hompes D, D'Hoore A, Van Cutsem E, et al. The Treatment of Peritoneal Carcinomatosis of Colorectal Cancer with Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) with Oxaliplatin: A Belgian Multicentre Prospective Phase II Clinical Study. Ann Surg Oncol.2012; 19: 2186-2194.

18- Hultman B, Lind P, Glimelius B, et al. Phase II study of patients with peritoneal carcinomatosis from gastric cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy. Acta Oncologica. 2012b; 52(4): 824-830.

19- Li C, Yan M, Chen J, et al. Surgical Resection With Hyperthermic Intraper.itoneal Chemotherapy for Gastric Cancer Patients With Peritoneal Dissemination. Journal of Surgical Oncology. 2010;102: 361-365.

20- Desantis MD, Bernard JL, Casanova V, et al. Morbidity, mortality, and oncological outcomes of 401 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC). langenbecks Arch Surg. 2015; 400: 37-48.

21- Yan, T.D., v Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience. Journal of Clinical Oncology. 2009;27(26): 6237-6242.

22- Wu, HT, Yang XJ, Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel to treat synchronous peritoneal carcinomatosis from gastric cancer: Results from a Chinese center. Eur J Surg Oncol. 2016;42: 1024-1034.

23- Turrini O, Lambaudie E, Faucher M, et al. Initial Experience With Hyperthermic Intraperitoneal Chemotherapy. Arch Surg. 2012;147(10): 919-923.

24- Chua, TC, Quinn LE, Zhao J, et al. Iterative Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Recurrent Peritoneal Metastases. Jorunal of Surgical Oncology. 2013;108: 81-88.

25- Wu, HT, Yang XJ, Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel improves survival for patients with peritoneal carcinomatosis from abdominal and pelvic malignancies. World Journal of Surgical Oncology.2016;14: 246-258.

26- Graziosi L, Marino E, De Angelis V, et al. Survival prognostic factors in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy treatment: analysis from a single oncological center. World Journal of Surgical Oncology.2016; 14: 97-106.

27- Vassos N, Förtsch T, Aladashvili A, et al. Repeated cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with recurrent peritoneal carcinomatosis. World Journal of Surgical Oncology. 2016;14: 42-51.

28- Shan LL, Saxena A, Shan BL, et al. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: A systematic review and meta-analysis. Surgical Oncology. 2014; 23: 199-210.

29- Tan WJ, Wong JFS, Chia CS, et al. Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: An Asian Perspective. Ann Surg Oncol. 2013;29: 4219-4223.

30- Tsilimparis, N., ve diğerleri. Quality of Life in Patients after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is It Worth the Risk?. Ann Surg Oncol.2013;20: 226-232.

31- Bakrin N, Bereder JM, Decullier E, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients. EJSO. 2013;39: 1435-1443.

32- Rettenmaier MA, Mendivil AA, Abaid LN, et al. Consolidation hyperthermic intraperitoneal chemotherapy and maintenance chemotherapy following laparoscopic cytoreductive surgery in the treatment of ovarian carcinoma. Journal of Hyperthermia.2015; 31(1): 8-14.

33- Di Giorgio A, Naticchioni E, Biacchi D, et al. Cytoreductive Surgery (Peritonectomy Procedures) Combined With Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

in the Treatment of Diffuse Peritoneal Carcinomatosis From Ovarian Cancer. Cancer. 2008;113(2): 315-326.

34- Deraco M, Virzı` S, Raspagliesi F, et al. Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study. Gynaecological Oncology. 2012. DOI 10.1111/j.1471-0528.2011.03207.x

35- Ansaloni L, Agnoletti V, Amadori A, et al. Evaluation of Extensive Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Patients With Advanced Epithelial Ovarian Cancer. International Journal of Gynecological Cancer. 2012;22(5).

36- Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, Giassas S. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015;22(5):1570-5.

6. Costs and Economic Assessment

6.1. Introduction

In this section, information on the costs of HIPEC and the results of the economic assessment will be presented within the scope of the findings obtained as a result of the systematic literature review. According to methodological approach further described in the section, answers to the questions in the section entitled costs and economic assessment in the STD Core Model are given. Besides data of systematic review, numeric data for use of HIPEC in Turkey are also presented, which are obtained from T.R. Ministry of Health Directorate General for Health Services (DGHS).

6.2. Assessment

As it is seen in the studies presented in the clinical effectiveness section, it has been shown that the life span of the patients is prolonged, complications encountered during the treatment process can be tolerated and the quality of life is improved over time by HIPEC with CRS. However, this treatment method is still a costly treatment for the health systems due to the length of hospital stay during the treatment process, the need for intensive care stay, cost of equipment and medications used, prolonged operation time and the like, and these costs should be compared to the positive changes in the life span and quality of life for the patients. Treatment is labor intensive and requires approximately 500 minutes of operation time, approximately 2-5 days of intensive care treatment and 7-23 days of hospitalization [1]. Although there is a limited number of studies with regard to the cost and cost efficiency of the treatment, the studies performed reveals the problems which have been encountered or will be encountered by the reimbursement agencies that come up against the decision to include the treatment in their positive lists due to high costs and additional high cost rates. An important issue to consider when evaluating the studies presented in this section is that each country identifies cost items and their calculation varies from country to country and from system to system. For this reason and because of differences in the methodology of the researches, it is not possible to compare the studies with each other. Studies on the cost of HIPEC with CRS can be grouped into three groups. In the first group, total and per patient costs of the treatment and their distribution among cost items were determined; in the second group, the effects of these costs on financing in various perspectives were evaluated; and in the third group, cost effectiveness analysis was performed.

In another study [1] to determine the total and average costs of treatment, the highest cost items were found as costs of service, operating room and intensive care as similar to the above. The study was a single-center, single-surgeon cost-benefit analysis conducted in a non-academic institution. The studies included 26 procedures applied to 25 patients received HIPEC treatment combined with CRS between June 2013 and August 2014. The average cost per patient in the study was $ 25.453.

A single-center study by Hinkle et al. [2] examined the cost data of 36 patients. The results of the analyses revealed that the average cost per patient in HIPEC treatment combined with CRS was 25,917$. 45% of direct costs account for operating room costs, manpower and anesthesia. Of the costs, 19% consisted of drugs, 8% consisted of laboratory tests, 7% consisted of blood, and 3% consisted of auxiliary services.

Studies examining the effect of costs due to HIPEC treatment with CRS on budget or financing have been the second type of studies conducted in this field. Squires et al. [3] investigated HIPEC treatment in combination with CRS for hospital financing and discussed the impact of the resulting costs depending on the type of reimbursement agency within the US health care system. In the study, hospital costs and reimbursement data were examined according to the type of insurance and post-operative costs. The study was a single-center study and included 64 patients treated between 2009 and 2013. When the patients were examined for tumor histology, it was found that 62% of them (n=40) were appendicular, 25% (n=16) were colorectal, 8% were (n= 5) goblet cell, and 5% (n=3) were mesothelioma. The mean hospital stay was 13 days and complications occurred in 66% (n = 42 patients) of the patients. 20% of complications (n = 13) are complications of grade III-IV. Of the patients enrolled in the study, 42 had private insurance, 22 had Medicare/Medicaid insurance and financial data of 56 patients were accessed. The average patient cost per patient was $ 49,248 and an amount of $63,771 was reimbursed per patient and the profit of the hospital per patient was calculated as $14,523. The costs of private insurance and Medicare/Medicaid patients are similar, but Medicare/Medicaid paid far less than private insurances ($30.713 versus $80.747; p<0,001) and caused financial loss of $ 17.342 per patient. Patients with private health insurance had serious complications and caused cost increases, resulting in net income of $36.285. In Medicare/Medicaid patients, there was a net loss of $54.274 due to complications. No statistically significant difference was found between patients' peritoneal cancer index score,

operation time, length of intensive care unit stay, mean duration of hospitalization and complication rates for insurance status. In the study, it was shown that serious complications significantly increase the average patient costs and the difference is statistically significant ($59.877 versus $46.650, p=0,01). The authors have concluded that treatment of CRS + HIPEC, an expensive treatment, is a profit-making treatment for the patients having private health insurance in USA, but is a kind of treatment which causes damage in terms of Medicare/Medicaid.

In a study by Bagnoli et al. [4], data of 24 patients, who received the treatment between September 2010 and May 2013, were evaluated in order to assess the sustainability and cost of HIPEC treatment in Italy having a system that makes payment depending on the diagnosis-related groups (DRG). In the analyzes, it was determined that the length of postoperative hospital stay and usage time for drug and material usage, and also operating room were the most important cost items affecting spending in HIPEC treatment combined with CRS. In the study, median length of hospital stay was 14 days, the median length of intensive care stay was 2-4 days, and median usage time of operating room was 585 minutes. Median expenditure per patient was € 21.744, and reimbursement of national health care system was €8.375. Distribution of expenditure according to cost items is presented in the table below.

Table 12: Expenditures and Amount of Reimbursement for HIPEC with CRS (€)[4]

Total Reimbursement		200.993 (100%)
General Costs		521.844 (259,6%)
Detailed Costs	Drug and Material Stay in Operating Room Hospital Stay Intensive Care Stay Manpower Common Costs Diagnosis and Services from Other Units Non-returned VAT Transfusion Services	125.400 (62,4%) 83.805 (41,7%) 74.906 (37,3%) 70.110 (34,9%) 50.413 (25,1%) 34,169 (17,0%) 33.235 (16,5%) 25.381 (12,6%) 24.425 (12,2%)
Gross Profit Margin		-320.851 -159,6%
Cases	Number	24
Postoperative Stay, Day	Median (range)	14 (10-30)
Intensive Care Stay, Day	Median (range)	2,4 (2-6)
Time for Operating Room (minute)	Median (range)	585 (377 -771)
Reimbursement Per Case	Median	8.375
Expenditure Per Case	Median	21.744

The authors have stated that as a result of the analyses, the amount of reimbursement for CRS + HIPEC in Italy health system could not meet the actual costs of the procedures and that this was a significant problem in terms of sustainability.

In a study conducted by Baratti et al. [5] in Italy, the financial data of 382 patients treated between 1995 and 2008 were retrospectively examined. In this study, reimbursement is made according to the DRG payment system. In the study, the average cost of hospital stay was 36.015 € and the average length of hospital stay was 24.3. Distribution of these costs is provided in Table 13. On the other hand, a total of €804.483 was paid for the services provided to the hospital and a gap of €1861.301 occurred for the period of two years. The authors have stated that for this treatment method that is not yet within the DRG system, a new coding should be developed immediately and a payment reflecting the real costs should be made.

Table 13: Distribution of Average Costs of HIPEC Treatment with CRS[5]

Cost Item	Cost (€)
Preoperative Stay	200,00
Intensive Care Stay	7.500,00
Postoperative Stay Postoperative Stay	3.600,00
Total Hospital Stay	**11.300,00**
Preoperative Research	**138,85**
Drugs	**1.622,92**
Stay in Operating Room	7.273,55
Personnel	2.360, 06
Disposal Materials	1.980,56
Equipment Amortization	450,00
HIPEC Disposal Materials	2.909,49
HIPEC Drugs	649,73
Blood Products	2.006,34
Total Surgical Combined Intervention	**17.629,73**
Postoperative Care	**1.180, 96**
General Expenses (%13)	**4.143,42**
Total	**36.015,89**

In the literature, cost-effectiveness analyses were carried out in the third group of studies performed for the cost of HIPEC treatment with CRS. Bonastre et al. [6] aimed in their study to determine the cost-effectiveness of palliative chemotherapy (standard) and HIPEC in peritoneal carcinomatosis caused by colorectal cancer. In the study, the data of 96 patients diagnosed with peritoneal carcinomatosis treated with HIPEC or palliative chemotherapy between January 1998 and December 2003 were examined. As a result of the study, it has been shown that HIPEC has improved survival and its cost is higher as compared to standard treatment. During the three-year observation period, it has been concluded that HIPEC achieved additional survival of 8.3 months and the Additional Cost Effectiveness Ratio (ACER) is € 58.086 (95% CI 35.893-112.839). When the disease severity of peritoneal carcinomatosis is taken into account, the authors have concluded that this intervention could be considered as a

cost effective intervention.

Hultman et al. [7] compared the cost effectiveness of neoadjuvant systemic chemotherapy and HIPEC combined with CRS in gastric cancer-induced peritoneal carcinomatous. Patients who had gastric cancer and received systemic chemotherapy, followed by HIPEC treatment combined with CRS and patients who only received systemic chemotherapy were compared for the results of intervention and costs. 10 patients included in the study were treated with CRS + HIPEC + EPIC and a control group of 10 patients with similar age, gender, performance status and similar characteristics with the patients in this group was created and the patients in this group was only administered systemic chemotherapy. The average overall survival for the intervention group was 20.5 months (range 6,0-34,3) and the median overall survival was 15.3 months. In the control group receiving only systemic treatment, the average overall survival was 11.1 months (range: 0.1-24.2 months) and median overall survival was 10.4 months. In the study, Quality Adjusted Life Years (QALY) was also calculated and QALY was 1,268 in the treatment group, while it was 0.774 (additional QALY 0.49) in the control group. The average cost per patient was $ 145,700 (95% CI $91,500 -$245.00) in the treatment group and was $ 59,300 (95% CI $45,500-73,800) in the control group. According to the distribution of the costs, treatment and post-treatment cost was higher in the treatment group, and the largest cost items were neoadjuvant chemotherapy ($ 6.300, 4% of costs), surgical procedure ($ 29.300, 20% of costs) and accordingly intensive care costs ($ 24.100, 17% of the costs). In the control group, the most important cost items were chemotherapy ($ 8,700, 15% of costs) and the related visits ($ 5,500, 9% of costs). According to the results obtained, the cost per QALY gained was found to be $ 175.164 (Table 14). The authors have noted that this result is above the threshold adopted by health systems in many countries, including Sweden, where the study was conducted, and they concluded that the intervention was not a cost effective intervention, according to the results of this study.

Table 14: Gained Life Year in HIPEC Treatment with CRS and Cost Per QALY[7]

	CRS+HIPEC+EPIC	Chemotherapy	Difference
Cost ($)	145.728	59.314	86.414
Life Year	1,45	0,93	0,52
QALY	1,27	0,77	0,49
Cost Per The Gained Life Year ($)			166.716
Cost Per QALY ($)			175.164

A third study of cost-effectiveness analysis in the systematic literature review was conducted by Chua et al. [8]. In this study, survival results of HIPEC treatment with CRS on malignant peritoneal surfaces and costs associated with treatment were compared in a tertiary agency in Australia. 159 CRS and HIPEC treatments conducted on 136 patients between June 2002 and June 2008 were included in the study. All procedures were performed by the same surgical team and the Sugarbaker peritonectomy procedures were used. After the cytoreduction, instillation of a chemoperfusate heated at approximately 42°C was performed intraabdominally for 90 minutes using coliseum technique. Mitomycin C (10-12,5 mg/m^2) was used for gastrointestinal malignancies, whereas cisplatin (50mg/m^2) and doxorubicin (12mg/m^2) were used for peritoneal mesothelioma and ovarian malignancies. Patients with pseudomyxoma peritonei and colorectal peritoneal carcinomatosis were scheduled to receive EPIC, 5-fluorouracil (680-800 m/m^2) from the first day to the fifth day after the operation as long as there is no clinical contraindication.

In this study [8], the total cost of 159 procedures during the six financial years was calculated as 10,556,463 Australian Dollars (AUD). AUD 663.275 (6%) of these costs were from clinical costs, , AUD 2.275.881 (22%) were from operating room costs, AUD 269.267 (3%) were from pathology costs, AUD 211.664 (2%) imaging costs, AUD 396.600 (23%) were from service stay, AUD 155.955 (2%) were from auxiliary health services, AUD 703.081 (7%) were from drug costs, AUD 272.238 (3%) were from prosthesis costs, AUD 264.495 (3%) were from amortization costs, AUD 646.137 (6%) were from continuing costs and AUD 2.699.047 (26%) were from intensive care costs. As seen, according to this study, the most important cost items among total costs are intensive care costs, inpatient service costs and operating room costs. The average cost per procedure was calculated as AUD 66.456 based on the

procedures performed during the six financial years and costs thereof. Considering the survival results and total treatment costs of CRS and HIPEC treatment, the cost per life year was calculated as AUD 37,737 for appendicular cancer, AUD 29,757 for colorectal cancer, AUD 29,559 for pseudomyxoma peritonei, AUD 20,521 for peritoneal mesothelioma and AUD 22,091 for the other peritoneal surface malignancies. Since the Australian National Health and Medical Research Council accepts the interventions between AUD 70,000 and AUD 100,000 per life year as cost-effective, the authors have noted that according to this threshold value, HIPEC combined with CRS could be considered as a cost-effective intervention, based on the recommendations of Australia authorities.

HIPEC is reimbursed by the Social Security Institution in Turkey with Communiqué on Healthcare Practices codes 604155 and P 604155 only at the Tertiary Training and Research Hospitals affiliated to the Ministry of Health. The reimbursement fee is TL 1,051,44 with the code 604155 for fee for service and TL 2.104,50 with the code P 604155 for diagnosis-related payment.

According to GDHS data, HIPEC has been applied to 76 patients in 2015 and to 125 patients in 2016 within the Social Security Institution payment in Turkey at the Tertiary training and research hospitals affiliated to the Ministry of Health. Distribution of these numbers by cities is presented in Table 15.

Table 15: Distribution for Turkey HIPEC Application

	2015	2016
Ankara	25	53
İstanbul	25	35
İzmir	14	11
Other	12	26
Total	76	125

According to the data provided by GDHS, medical consumables of TL 897.390 were purchased for HIPEC during the period of 2015-2016 according to the records of T. R Health Material Recording Management System. No detailed analysis has been done

for staff, drugs and other expenses. However, when calculated according to diagnosis-related procedure score, possible SSI reimbursement for 201 patients was estimated as TL 423.004 during the period of 2015-2016. In this context, the Ministry of Health is estimated to spend an additional TL 2.360 per patient with the HIPEC treatment, excluding personnel, medicine and other expenses. It can be said that much more additional expenditure is made when personnel, medicine and other expenses are added to this cost.

6.3. Discussion and Result

In the systematic literature review, seven studies about the cost and cost effectiveness of HIPEC treatment with CRS were obtained. Some of these studies aimed to assess the impact of intervention on total and average costs, some on hospital funding, others on cost effectiveness. Since treatment is an expensive treatment, there is a significant impact of such analyzes for the decisions of the reimbursement agencies, especially those planning to include the treatment in the reimbursement list.

The greatest cost items in HIPEK treatment with CRS were found to be operating room costs, and the length of hospital stay and intensive care stay. It is not a correct approach to compare the results of the studies with each other in terms of average costs and come to a conclusion because the costs vary depending upon the dynamics of each health system, calculation methods used in the studies and the mode of treatment. The average cost was AUD 66.456 in a study conducted in Australia [8], the average cost was $25.453 in a study carried out in the USA [1], the average cost was $25,917 in a study carried out by Hinkle et al. [2]in the USA, and the average cost was $49,248 in a study conducted by Squires et al. [3] in USA.

An important consequence of the literature review is that the reimbursed amount of money does not meet the real costs and puts additional financial burden on the hospital, in the case that payments are done according to diagnosis-related groups (DRG) in two different countries (USA and Italy) [3,4,5]. These results suggest that the cost of the intervention should be calculated correctly for reimbursement decisions and the amount of reimbursement must be determined accordingly.

Two studies have been found, which analyze the cost effectiveness of HIPEC with CRS use in the treatment of peritoneal carcinomatosis [6,7]. In one of the studies [6] it has been stated that the cost of the ICER obtained is a cost effective option given

the severity of the disease and the in the other study [7] it has been indicated that the ICER is not a cost effective option as its cost is too high and it exceeds the Swedish reimbursement threshold. These results once again demonstrate that cost-effectiveness analyses should be evaluated in a country-specific manner within the context of their own cost and health system dynamics under each country's conditions.

Although there is not a cost effectiveness analysis conducted in Turkey, it has been observed that the HIPEC treatment has begun to be widespread in the light of GDHS's data. Cost data have begun to be created as it spreads. It has been observed in the light of the available data that the Ministry of Health adopts a policy which provides service under the reimbursement amount in order to improve the health of critically-ill patients. It is beneficial to carry out further cost-effectiveness analyzes in the light of the resulting data.

6.4. References

1- Naffouje SA, O`Donoghue C, and George I. Evaluation of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in a Community Setting: A Cost-Utility Analysis of a Hospital's Initial Experience and Reflections on the Health Care System. Journal of Surgical Oncology. 2016;113: 544-547.

2- Hinkle NM, MacDonald J, Sharpe JP, et al. Cytoreduction with hyperthermic intraperitoneal chemotherapy: an appraisal of outcomes and cost at a newly established peritoneal malignancy program. The American Journal of Surgery.2016; 212: 413-418.

3- Squires MH, Staley CA, Knechtle W, et al. Association Between Hospital Finances, Payer Mix, and Complications After Hyperthermic Intraperitoneal Chemotherapy: Deficiencies in the Current Healthcare Reimbursement System and Future Implications. Ann Surg Oncol.2016; 22: 1739-1745.

4- Bagnoli PF, Cananzi FCM, Brocchi A, et al. Peritonectomy and hyperthermic intraperitoneal chemotherapy: Cost analysis and sustainability. EJSO.2015; 41: 386-391.

5- Baratti D, Scivales A, Balestra MR, et al. Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). EJSO. 2010;36: 463-469.

6- Bonastre J, Chevalier J, Elias D, et al. Cost-Effectiveness of Intraperitoneal Chemohyperthermia in the Treatment of Peritoneal Carcinomatosis from Colorectal Cancer. Value in Health. 2008;11(3): 347-353).

7- Hultman B, Lundkvist J, Glimelius B, et al. Costs and clinical outcome of neoadjuvant systemic chemotherapy followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from gastric cancer. Acta Oncologica. 2011;51(1): 112-121.

8- Chua, TC, Martin S, Cert G, et al. Evaluation of the Cost-Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (Peritonectomy) at the St George Hospital Peritoneal Surface Malignancy Program. Ann Surg. 2010;251: 323-329.

7. Organizational Aspects of Hyperthermic Intraperitoneal Chemotherapy

7.1. Introduction

In this section, information on the organizational aspects of HIPEC will be presented within the scope of the findings obtained as a result of the systematic literature review. Answers to the questions in the section titled organizational aspects in HTA Core Model were given within the scope of the methodological approach that was further described in the section.

7.2. Assessments

As seen in review so far, HIPEC with CRS is a complex intervention and requires a multidisciplinary team approach. This team should be consisted of oncology surgeons, anesthesiologists, perfusionists (optionally), pharmacists, nurses and support personnel (such as physiotherapists, psychologists, nutritionists), pathologists and research personnel, according to the clinical guidelines developed by Canada HIPEC Collaborative Group. These personnel should be in the institution where the intervention is made and intervene when necessary. The team leader is a surgeon, and other team members (such as medical oncologists, gastroenterologists) should preferably be in the same institution, but should be a member of a common network to be contacted as needed in the case that they are not in the institution. The surgeon must have oncologic surgery training, as well as CRS surgery and HIPEC treatment trainings, and in addition, should have researches and studies about peritoneal surface malignancies. In the guideline, although annual minimum number of treatment per surgeon has not been specified, but it has been stated that a center or team should perform at least 20 operations annually [1].

As can be seen from the researches presented in the safety and clinical effectiveness sections, morbidity rates vary between 11-50% and mortality rates vary between 0-10% in the initial treatment reports in the HIPEC treatment combined with CRS. By the subsequent administration of treatment, morbidities developed with experience and an evidence for the presence of a learning curve was revealed. At the same time, the effect of the learning curve is also seen in complete cytoreduction and in the length of hospital stay. For example, Kuijpers et al. [2] aimed to determine the importance of the learning curve by comparing the data of the first 100 treatments of the three

centers that have just begun to apply the HIPEC treatment combined with CRS to the data of the first 100 treatments of an experienced leading hospital. A total of 372 cases from four institutions were examined. All cases were conducted following the same treatment protocol. The new centers participating in the study were trained for the first ten cases by the leading center at the beginning of the operation and thus began to conduct the treatment with more experience and information as compared to the leading institution. This training has been shown to have a positive effect on the results of the new institutions. For example, macroscopic complete cytoreduction was conducted in 86% of patients in the new centers, whereas this ratio was found to be 66% at the leading center ($p<0,001$). The authors have concluded that not only these trainings, but also the new knowledge and experience that have developed in relation to this treatment method in the world are also effective for the results of the new centers.

Voron et al. [3] conducted a study to assess the learning curve of HIPEC combined with CRS and determine variables related to morbidity and oncologic outcomes at a newly specialized surgery center. In the study, the data of 291 patients operated between September 2006 and December 2012 were examined. 114 of the patients were colorectal, 14 were pseudomycosis peritonei, 38 were mesothelioma, 15 were gastric and 23 were overian-originated. In the study, complete CRS rate was reported as 70.4%, serious morbidity as 30.4% and mortality as 2.5%. The causes of incomplete cytoreduction were found as tumor histotype, high peritoneal cancer index and occupied area, whereas the causes of serious morbidity were previous surgical operation, stoma and blood transfusion. As a result of the analyses, it is stated that at least 140 operations should be performed to reduce the risk of incomplete cytoreduction and at least 40 operations should be performed to decrease the serious morbidity risk. Turrini et al. (2012) [4] noted a significant reduction in grade III / IV morbidity, perioperative transfusions and reoperations after 20 operations.

In a study by Mohamed and Moran [5], the relationship between mortality and morbidity, and the learning curve in HIPEC treatment combined with CRS was discussed. The table below presents the mortality and morbidity data obtained from various studies. As stated by the authors, it is difficult to compare these data because of the lack of a unity in the morbidity rating methods although morbidity and mortality ratios are higher in the first studies than those in the subsequent studies. The authors state that this development can be explained by the concept of ‘learning curve’.

Table 16: Relationship Between Mortality and Morbidity, and Learning Curve in the HIPEC Treatment Combined with CRS[5]

Study	Year	Patient	Treatment	Morbidity (%)	Mortality (%)
Witkamp et al.	2001	46	HIPEC (MMC)	39	9
Guner	2005	28	HIPEC (MMC or Cisplatin)	36	7
Loungnarath et al.	2005	27	HIPEC (MMC or Cisplatin)	22	0
Miner et al.	2005	97	IV/EPIC 5FU (4 patients HIPEC)	16	4
Sugarbaker et al.	2006	356	HIPEC (MMC)+ EPIC (5FU)	19	2
Stewart et al.	2006	110	HIPEC (MMC)	38	6
Yan et al.	2006	60	HIPEC (MMC)+ EPIC (5FU)	12	4
Murphy et al.	2007	123	HIPEC (MMC)+ EPIC (5FU)	21	5
Smeenk et al.	2007	103	HIPEC (MMC)	54	3
Baratti et al.	2008	95	HIPEC (MMC and Cisplatin)	18,7	1
Elias et al.	2008	105	HIPEC (MMC/ox/irino/ind IV 5FU)	67,6	7,8
Median (Range)				31 (12-67,6)	4 (0-9)

MMC: Mitomycin C, ox: Oxaliplatin, irino: irinotecan, ind: induction

As can be seen, one of the most important factors for the organizational aspects of HIPEC treatment is the learning curve, and it is necessary that teams receive necessary training and have performed a certain number of operations in order to reach a certain level of success of treatment which is a health care service provided by the institutions where tertiary health services are offered.

As discussed in the safety section of this study, the safety of teams who perform the treatment process in the HIPEC treatment with CRS appears to be one of the important issues. Ensuring the safety of teams is one of the most important issues that the institution where the treatment is conducted should focus on organizationally. In this context, it is also an important that which steps of the procedure is performed and by whom. Ferron et al. [6] conducted a study on 33 surgical teams who perform this treatment method in France to examine the management of risk of environmental contamination of HIPEC procedures, protective equipment of the personnel performing the procedure, or aspects of occupational hazard control. 14 of these teams have experience of HIPEC for longer than 10 years. The teams participating

in the study prefer closed abdominal procedures instead of open ones (76%) and 10 teams do not use any protection method when open abdomen technique is applied, while the others use a special kit (n=5), a transparent adhesive curtain (n=5), a plastic ring curtain (n=3), an intestine bag (n=3) and a cytotoxic extractor (n=3). All of the teams use the European Union approved HIPEC machine and the preparation and use of the system is done by a biomedical engineer (n = 11), a surgical nurse (n = 23), an anesthetist (n = 3) or a surgeon (n = 7). In the majority of the teams (n = 23), only one surgeon performs all operations. The teams are kept particularly small after chemotherapy injection and in some programs people of less than 3 (n = 11) and less than 5 (n = 22) are left in the operating room. Table 17th summarizes the procedures during the use of chemotherapy and persons who perform them.

Table 17: Chemotherapy Procedures in the HIPEC Treatment with CRS[6]

		N	%
Simultaneous IV Injection	- Yes - No	25 8	76 24
Who prescribes the chemotherapy?	- Surgeon - Medical oncologist - Anesthetist	21 17 1	63,6 51,5 3
Who controls the dose?	- Pharmacist - Medical oncologist - Surgeon - Surgical nurse - Anesthetist - No control	14 7 9 3 3 1	42,4 21,2 27,3 9 9 3
Packaging of wastes	-Special garbage for the potentially infected clinical waste - Special cytotoxic garbage - Special box for the potentially infected clinical waste	26 3 3	78,8 9 9
Waste disposal	- Cytotoxic cycle (1200^{0}C) - Cycle for the potentially infected clinical waste (850^{0}C) - Not aware of cycle	13 13 10	39,4 39,4 30,3

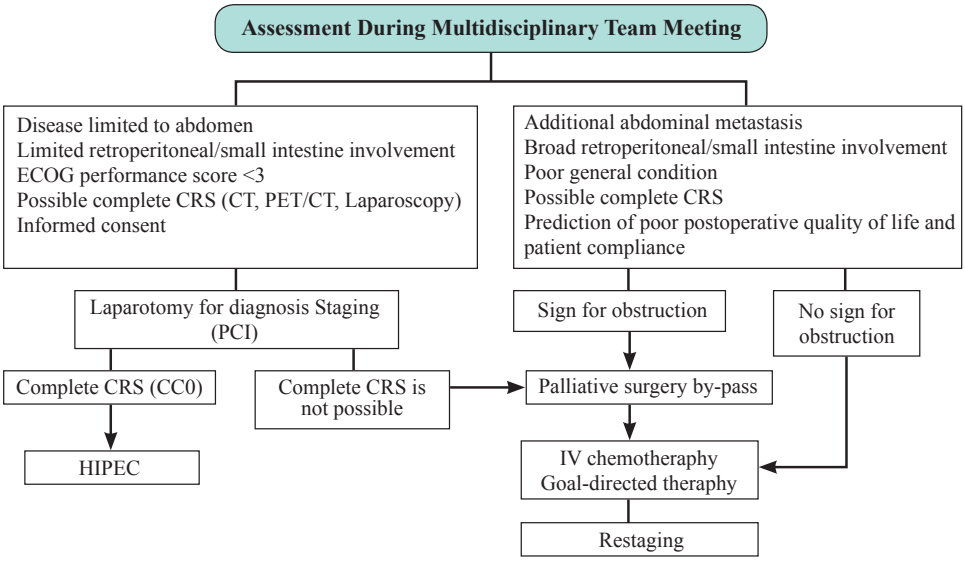
According to the results of the study, the operating room was ventilated with a laminar flow system (n=18) by many teams and 14 out of 33 teams stated that they were informed about this ventilation and that they checked ventilation standards hourly. Table 18th presents the main safety guidelines for HIPEC.

Table 18: Main Safety Guidelines for HIPEC [6]

Equipment-Status-Procedure	Main Risk	Recommendation
Personal Protective Equipment - Two pairs of gloves - Eyeglasses for eye protection - High-grade filter mask	Skin contact Splash of chemotherapeutic agents Surgical vapor	***** *****
Protective Procedures in the Operating Room - Emergency standard operation procedures for splashing	- Splash of chemotherapeutic agents	*****
Ventilation for the Operating Room - Laminar flow system - HEPA filter	- Surgical vapors	**** ****
HIPEC Procedures - Closed abdominal procedure	- Skin contact, splash of chemotherapeutic agents	****
Waste Management - Cycle with special infected clinical waste and burning (850-1200^{0}C)	Contamination	****
Special Technique Training	Dysfunction	****
Recording by Occupational Health Unit	Not reporting the events	****

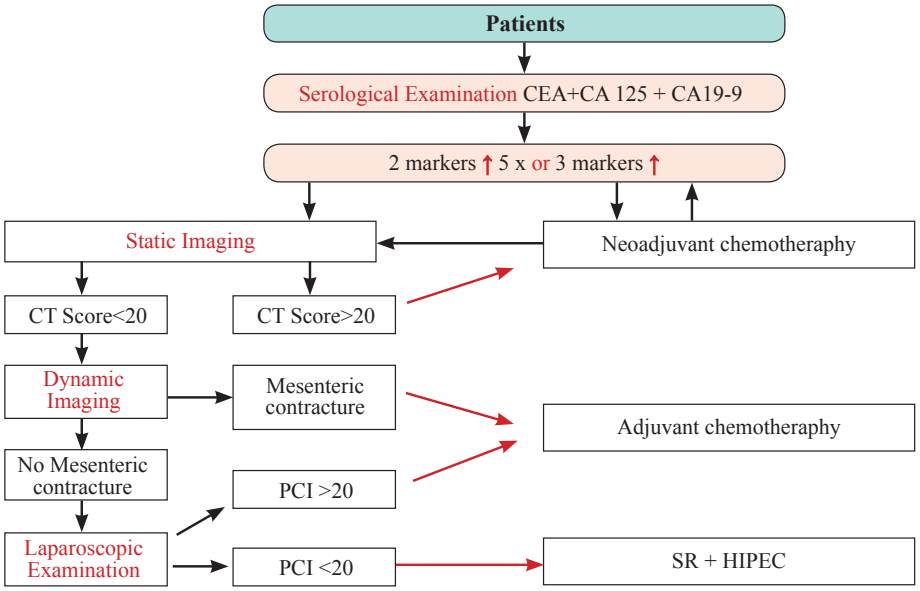
There is no general consensus on how patient flow will be due to the lack of developed and generally accepted treatment guidelines in the HIPEC technology with CRS. In the following scheme, a patient algoritm was presented, which is used at a center for the patient flow in the systematic literature analysis [7].

Figure 5: Treatment Algorithm for HIPEC Treatmt with CRS[7]



However, this algorithm is an algorithm defined at a center, and there is no algorithm in guidelines and international practice, for which a compromise is reached. A similar algorithm was developed by Li et al. [8] (Figure 6).

Figure 6: Clinical Treatment Algorithm for the Treatment of Peritoneal Carcinomatosis[8]



7.3. Discussion and Result

In the systematic literature analysis of HIPEC treatment with CRS in peritoneal carcinomatosis, it has been revealed that the main subject matters are the learning curve, the safety of treatment teams and the job descriptions when the subject matters discussed for the organizational aspects are considered. Studies have shown the importance of the learning curve and an improvement of the mortality and morbidity rates after a certain number of procedures have been reported.

7.4. References

1- Dubé P, Sideris L, Law C, et al. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms. Curr Oncol. 2015; 22:100-112.

2- Kuijpers AM, Hauptmann M, Aalbers AG, et al. Cytoreduction and hyperthermic intraperitoneal chemotherapy: The learning curve reassessed. EJSO. 2016; 42: 244-250.

3- Voron T, Eveno C, Jouvin I, et al. Cytoreductive surgery with a hyperthermic intraperitoneal chemotherapy program: Safe after 40 cases, but only controlled after 140 cases. EJSO. 2015; 41: 1671-1677.

4- Turrini O, Lambaudie E, Faucher M, et al. Initial Experience With Hyperthermic Intraperitoneal Chemotherapy. Arch Surg.2012; 147(10): 919-923.

5- Mohamed F and Moran BJ. Morbidity and Mortality With Cytoreductive Surgery and Intraperitoneal Chemotherapy The Importance of a Learning Curve. Cancer J. 2009;15: 196–199, ISSN: 1528-9117/09/1503-0196.

6- Ferron G, Simon L, Guyon F, et al. Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey. EJSO.2015; 41: 1361-1367.

7- Topgul, K, Cetinkaya MB, N. Arslan NC, et al. Cytoreductive surgery (SRC) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal carcinomatosis: Our initial experience and technical details. Ulus Cerrahi Derg. 2015;31:138-147.

8- Li Y, Zhou YF, Liang H, et al. Chinese expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies. World Jorunal of Gastroenterology. 2016;22(30): 6906-6916.

ANNEX 1: List of Articles Determined After Systematic Literature Review and On Which the Study is Based

1. Terence C. Chua, Samantha Martin, Grad Cert, Akshat Saxena, Winston Liauw, Tristan D. Yan, Jing Zhao, Irene Lok and David L. Morris, "Evaluation of the Cost-Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (Peritonectomy) at the St George Hospital Peritoneal Surface Malignancy Program", Ann Surg 2010;251: 323–329, DOI: 10.1097/SLA.0b013e3181c9b53c (Ref 1)

2. SAMER A. NAFFOUJE, CRISTINA O'DONOGHUE, AND GEORGE I. SALTI, "Evaluation of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in a Community Setting: A Cost-Utility Analysis of a Hospital's Initial Experience and Reflections on the Health Care System, J. Surg. Oncol. 2016;113:544–547. DOI 10.1002/jso.24162 (REF 2)

3. H.-T. Wu, K.-W. Peng, Z.-H. Ji , J.-H. Sun, Q. Zhang, X.-J. Yang, C.-Q. Huang, Y. Li, "Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy with lobaplatin and docetaxel to treat synchronous peritoneal carcinomatosis from gastric cancer: Results from a Chinese center", EJSO 42 (2016) 1024-1034, http://dx.doi.org/10.1016/j.ejso.2016.04.053. (Ref 3)

4. P.H. Sugarbaker, D. Chang, "Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival", EJSO 43 (2017) 1228-1235, http://dx.doi.org/10.1016/j.ejso.2017.01.009. (Ref 4)

5. P.A. Cascales-Campos, P.A. Sanchez-Fuentes, J. Gil, E. Gil, V. Lopez-Lopez, N. Rodriguez Gomez-Hidalgo, D. Fuentes, P. Parrilla, "Effectiveness and failures of a fast track protocol after cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy in patients with peritoneal surface malignancies", Surgical Oncology 25 (2016) 349-354, http://dx.doi.org/10.1016/j.suronc.2016.08.001. (Ref 5)

6. Simon Rodier, Guillaume Saint-Lorant, Jean-Marc Guilloit, Agn_es Palix, Fabienne Divanon, François Sichel, Raphaєl Del_ep_ee, "Is hyperthermic intraperitoneal chemotherapy (HIPEC) safe for healthcare workers?, Surgical Oncology 26 (2017) 242-251, http://dx.doi.org/10.1016/j.suronc.2017.04.001. (Ref 6)

7. Francisco C. Mun˜oz-Casares, Sebastia´n Rufia´n, A ´ lvaro Arjona-Sa´nchez, Marı´a J. Rubio, Rafael Dı´az, A ´ngela Casado, A´ lvaro Naranjo, Carlos J. Dı´az-Iglesias, Rosa Ortega, Marı´a C. Mun˜oz-Villanueva, Jordi Muntane´, Enrique Aranda, "Neoadjuvant intraperitoneal chemotherapy with paclitaxel for the radical surgical treatment of peritoneal carcinomatosis in ovarian cancer: a prospective pilot study", Cancer Chemother Pharmacol (2011) 68:267–274, DOI 10.1007/s00280-011-1646-4 (Ref 7)

8. Hidde J. Braam, Djamila Boerma, Marinus J. Wiezer, Bert van Ramshorst, "Cytoreductive surgery and HIPEC in treatment of colorectal peritoneal carcinomatosis: experiment or

standard care? A survey among oncologic surgeons and medical oncologists", Int J Clin Oncol (2015) 20:928–934. DOI 10.1007/s10147-015-0816-5 (Ref 8)

9. Jingxu Sun, Yongxi Song, Zhenning Wang, Peng Gao, Xiaowan Chen, Yingying Xu, Jiwang Liang and Huimian Xu, "Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials", BMC Cancer 2012, 12:526-536, http://www.biomedcentral.com/1471-2407/12/526 (Ref 9)

10. Charlotte E L Klaver, Gijsbert D Musters, Willem A Bemelman, Cornelis J A Punt, Victor J Verwaal3, Marcel GW Dijkgraaf, Arend GJ Aalbers, Jarmila DW van der Bilt, Djamila Boerma, Andre JA Bremers, Jacobus WA Burger, Christianne J Buskens, Pauline Evers, Robert J van Ginkel, Wilhelmina MU van Grevenstein, Patrick HJ Hemmer, Ignace HJT de Hingh, Laureen A Lammers, Barbara L van Leeuwen9, Wilhelmus JHJ Meijerink13, Simon W Nienhuijs, Jolien Pon, Sandra A Radema, Bert van Ramshorst, Petur Snaebjornsson, Jurriaan B Tuynman, Elisabeth A te Velde, Marinus J Wiezer, Johannes HW de Wilt and Pieter J Tanis, "Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial", "BMC Cancer (2015) 15:428-437. DOI 10.1186/s12885-015-1430-7 (Ref 10)

11. Tristan D. Yan, Deborah Black, Paul H. Sugarbaker, Jacqui Zhu, Yutaka Yonemura, George Petrou, and David L. Morris, "A Systematic Review and Meta-analysis of the Randomized Controlled Trials on Adjuvant Intraperitoneal Chemotherapy for Resectable Gastric Cancer", Annals of Surgical Oncology (2007) 14(10):2702–2713. DOI: 10.1245/s10434-007-9487-4 (Ref 11)

12. Enrico Facchiano, Domenico Risio, Reza Kianmanesh, and Simon Msika, "Laparoscopic Hyperthermic Intraperitoneal Chemotherapy: Indications, Aims, and Results: A Systematic Review of the Literature", Ann Surg Oncol (2012) 19:2946–2950. DOI 10.1245/s10434-012-2360-0 (Ref 12)

13. Thijs R. van Oudheusden, Hidde J. Braam, Simon W. Nienhuijs, Marinus J. Wiezer, Bert van Ramshorst, Misha D. Luyer, Valery E. Lemmens, and Ignace H. de Hingh, "Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy: A Feasible and Effective Option for Colorectal Cancer Patients After Emergency Surgery in the Presence of Peritoneal Carcinomatosis", Ann Surg Oncol (2014) 21:2621–2626, DOI 10.1245/s10434-014-3655-0, (Ref 13)

14. YUKA FUJISHIMA, TAKANORI GOI, YOUHEI KIMURA, YASUO HIRONO, KANJI KATAYAMA and AKIO YAMAGUCHI, "MUC2 protein expression status is useful in assessingthe effects of hyperthermic intraperitoneal chemotherapyfor peritoneal dissemination of colon cancer", INTERNATIONAL JOURNAL OF ONCOLOGY (2012) 40: 960-964, DOI: 10.3892/ijo.2012.1334. (Ref 14)

15. Bo Hultman, Pehr Lind, Bengt Glimelius, Magnus Sundbom, Peter Nygren, Ulf Haglund & Haile Mahteme, "Phase II study of patients with peritoneal carcinomatosis from gastric

cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy", Acta Oncologica (2013), 52:4, 824-830, DOI:10.3109/0284186X.2012.702925. (REF 15)

16. Deng-Hai Mi, Zheng Li, Ke-Hu Yang, Nong Cao, Anne Lethaby, Jin-Hui Tian, Nancy Santesso, Bin Ma, Yao-Long Chen & Ya-Li Liu, "Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: A systematic review and metaanalysis of randomised controlled trials", International Journal of Hyperthermia (2013), 29:2, 156-167, DOI: 10.3109/02656736.2013.768359. (REF 16)

17. Julia Bonastre, Julie Chevalier, Dominique Elias, Jean Marc Classe, Gwenaël Ferron, Jean Marc Guilloit, Frédéric Marchal, Pierre Meeus, Gerard De Pouvourville, "Cost-Effectiveness of Intraperitoneal Chemohyperthermia in the Treatment of Peritoneal Carcinomatosis from Colorectal Cancer", International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 1098-3015/08/347 347–353, 10.1111/j.1524-4733.2007.00249.x. (REF 17)

18. Shigeki Kusamura, Dario Baratti, Rami Younan, Barbara Laterza, Grazia Daniela Oliva, Pasqualina Costanzo, Myriam Favaro, Cecilia Gavazzi, Federica Grosso, and Marcello Deraco, "Impact of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Systemic Toxicity", Annals of Surgical Oncology 14(9):2550–2558, DOI: 10.1245/s10434-007-9429-1. (REF 18)

19. Gitonga Munene, Lloyd A. Mack, and Walley J. Temple, "Systematic Review on the Efficacy of Multimodal Treatment of Sarcomatosis with Cytoreduction and Intraperitoneal Chemotherapy", Ann Surg Oncol (2011) 18:207–213, DOI 10.1245/s10434-010-1229-3. (REF 19)

20. Dario Baratti, Shigeki Kusamura, Elvira Mingrone, Maria Rosaria Balestra, Barbara Laterza, and Marcello Deraco, "Identification of a Subgroup of Patients at Highest Risk for Complications After Surgical Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy", Ann Surg 2012;256: 334–341, DOI: 10.1097/SLA.0b013e31825704e3. (REF 20)

21. Angelo Di Giorgio, Enzo Naticchioni, Daniele Biacchi, Simone Sibio, Fabio Accarpio, Monica Rocco, Sergio Tarquini, Marisa Di Seri, Antonio Ciardi, Daniele Montruccoli, Paolo Sammartino, "Cytoreductive Surgery (Peritonectomy Procedures) Combined With Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Diffuse Peritoneal Carcinomatosis From Ovarian Cancer", Cancer 2008;113:315–25, DOI 10.1002/cncr.23553. (REF 21)

22. Faheez Mohamed, and Brendan J. Moran, "Morbidity and Mortality With Cytoreductive Surgery and Intraperitoneal Chemotherapy The Importance of a Learning Curve", Cancer J 2009;15: 196–199, ISSN: 1528-9117/09/1503-0196. (REF 22)

23. R Mirnezami, A M Mehta, K Chandrakumaran, T Cecil, B J Moran, N Carr, V J Verwaal, F Mohamed and A H Mirnezami, “Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone”, British Journal of Cancer (2014) 111, 1500–1508, doi: 10.1038/bjc.2014.419. (REF 23)

24. P. Dubé md, L. Sideris, C. Law, L. Mack, E. Haase, C. Giacomantonio, A. Govindarajan, M.K. Krzyzanowska, P. Major, Y. McConnell, W. Temple, R. Younan and J.A. McCart, “Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms” Curr Oncol, Vol. 22, pp. e100-112; doi: http://dx.doi.org/10.3747/co.22.2058. (REF 24)

25. Please cite this paper as: Deraco M, Virzı` S, Raspagliesi F, Iusco D, Puccio F, Macrı` A, Famulari C, Solazzo M, Bonomi S, Grassi A, Baratti D, Kusamura S. “Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study”, BJOG 2012;119:800–809, DOI: 10.1111/j.1471-0528.2011.03207.x. (REF 25)

26. Luca Ansaloni, Vanni Agnoletti, Andrea Amadori, Fausto Catena, Davide Cavaliere, Federico Coccolini, Pierandrea De Iaco, Monica Di Battista, Massimo Framarini, Filippo Gazzotti, Claudio Ghermandi, Barbara Kopf, Maristella Saponara, Francesca Tauceri, Carlo Vallicelli, Giorgio Maria Verdecchia, and Antonio Daniele Pinna, “Evaluation of Extensive Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Patients With Advanced Epithelial Ovarian Cancer”, Int J Gynecol Cancer 2012;22: 778Y785, DOI: 10.1097/IGC.0b013e31824d836c. (REF 26)

27. Tristan D. Yan, Marcello Deraco, Dario Baratti, Shigeki Kusamura, Dominique Elias, Olivier Glehen, Franc¸ois N. Gilly, Edward A. Levine, Perry Shen, Faheez Mohamed, Brendan J. Moran, David L. Morris, Terence C. Chua, Pompiliu Piso, and Paul H. Sugarbaker, “Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience”, J Clin Oncol 27:6237-6242, DOI: 10.1200/JCO.2009.23.9640. (REF 27)

28. CHEN LI, MIN YAN, JUN CHEN, MIN XIANG, ZHENG GANG ZHU, HAO RAN YIN, AND YAN ZHENG LIN, “Surgical Resection With Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer Patients With Peritoneal Dissemination”, J. Surg. Oncol. 2010;102:361–365, DOI 10.1002/jso.21628. (REF 28)

29. Nathan M. Hinkle, James MacDonald, John P. Sharpe, Paxton Dickson, Jeremiah Deneve, D.O., Gitonga Munene, “Cytoreduction with hyperthermic intraperitoneal chemotherapy: an appraisal of outcomes and cost at a newly established peritoneal malignancy program”, The American Journal of Surgery (2016) 212, 413-418, http://dx.doi.org/10.1016/j.

amjsurg.2016.01.022. (REF 29)

30. Y. Liu, A. Mizumoto, H. Ishibashi, K. Takeshita, M. Hirano, M. Ichinose, S. Takegawa, Y. Yonemur, “Should total gastrectomy and total colectomy be considered for selected patients with severe tumor burden of pseudomyxoma peritonei in cytoreductive surgery?”, EJSO 42 (2016) 1018-1023, http://dx.doi.org/10.1016/j.ejso.2016.04.059. (REF 30)

31. Leonard L. Shan, Akshat Saxena, Bernard L. Shan, David L. Morris, “Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: A systematic review and meta-analysis”, Surgical Oncology 23 (2014) 199-210, http://dx.doi.org/10.1016/j.suronc.2014.10.002. (REF 31)

32. T. Voron, C. Eveno, I. Jouvin, A. Beaugerie, R. Lo Dico, S. Dagois, P. Soyer, M. Pocard, “Cytoreductive surgery with a hyperthermic intraperitoneal chemotherapy program: Safe after 40 cases, but only controlled after 140 cases”, EJSO 41 (2015) 1671e1677, http://dx.doi.org/10.1016/j.ejso.2015.09.005. (REF 32)

33. Shigeki Kusamura, Dario Baratti, Rami Younan, And Marcello Deraco, “The Delphi Approach to Attain Consensus in Methodology of Local Regional Therapy for Peritoneal Surface Malignancy”, Journal of Surgical Oncology 2008;98:217–219, DOI 10.1002/jso.21059. (REF 33)

34. Olivier Turrini, Eric Lambaudie, Marion Faucher, Fre´de´ric Viret, Jean Louis Blache, Gilles Houvenaeghel, Jean Robert Delpero, “Initial Experience With Hyperthermic Intraperitoneal Chemotherapy”, Arch Surg. 2012;147(10):919-923, doi:10.1001/archsurg.2012.988. (REF 34)

35. Richard Sleightholm, Jason M. Foster, Lynette Smith, Wim Ceelen, Marcello Deraco, Yusuf Yildirim, Edward Levine, Cristobal Mu~ Noz-Casares, Olivier Glehen, Asish Patel, And Jesus Esquivel, “The American Society of Peritoneal Surface Malignancies Multi-Institution Evaluation of 1,051 Advanced Ovarian Cancer Patients Undergoing Cytoreductive Surgery and HIPEC: An Introduction of the Peritoneal Surface Disease Severity Score”, J. Surg. Oncol. 2016;114:779–784, DOI 10.1002/jso.24406. (REF 35)

36. Mehraneh D. Jafari, Wissam J. Halabi, Michael J. Stamos, Vinh Q. Nguyen, Joseph C. Carmichael, Steven D. Mills, Alessio Pigazzi, “Surgical Outcomes of Hyperthermic Intraperitoneal Chemotherapy Analysis of the American College of Surgeons National Surgical Quality Improvement Program”, JAMA Surg. 2014;149(2):170-175. doi:10.1001/jamasurg.2013.3640. (REF 36)

37. S. Scaringi, R. Kianmanesh, J.M. Sabate, E. Facchiano, P. Jouet, B. Coffin, G. Parmentier, J.M. Hay, Y. Flamant , S. Msika, “Advanced gastric cancer with or without peritoneal carcinomatosis treated with hyperthermic intraperitoneal chemotherapy: A single western center experience”, EJSO 34 (2008) 1246e1252, doi:10.1016/j.ejso.2007.12.003. (REF 37)

38. Geert A. Simkens, Vic J. Verwaal, Valery E. Lemmens, Harm J. Rutten, Ignace H. de Hingh," Short-term outcome in patients treated with cytoreduction and HIPEC compared to conventional colon cancer surgery", Medicine (2016) 95:41(e5111), http://dx.doi.org/10.1097/MD.0000000000005111. (REF 38)

39. Nayef Alzahrani, Jorgen S. Ferguson, Sarah J. Valle, Winston Liauw, Terence Chua and David L. Morris, "Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: long-term results at St George Hospital, Australia, ANZ" J Surg 86 (2016) 937–941, doi: 10.1111/ans.13152. (REF 39)

40. Bo Hultman, Jonas Lundkvist, Bengt Glimelius, Peter Nygren & Haile Mahteme, "Costs and clinical outcome of neoadjuvant systemic chemotherapy followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from gastric cancer", Acta Oncologica (2012), 51:1, 112-121, DOI: 10.3109/0284186X.2011.594809. (REF 40)

41. John H Stewart, Perry Shen and Edward A Levine, "Intraperitoneal hyperthermic chemotherapy: an evolving paradigm for the treatment of peritoneal surface malignancies", Expert Rev. Anticancer Ther. (2008), 8(11), 1809–1818, 10.1586/14737140.8.11.1809. (REF 41)

42. Jesus Esquivel, Pompiliu Piso, Vic Verwaal, Thomas Bachleitner-Hofmann, Olivier Glehen, Santiago Gonza´ Lez-Moreno, Marcello Deraco, Joerg Pelz, Richard Alexander, And Gabriel Glockzin, "American Society of Peritoneal Surface Malignancies Opinion Statement on Defining Expectations from Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Patients with Colorectal Cancer", Journal of Surgical Oncology 2014;110:777–778, DOI 10.1002/jso.23722. (REF 42)

43. Geert A. Simken, Thijs R. van Oudheusden, Hidde J. Braam, Misha D. Luyer, Marinus J. Wiezer, Bert van Ramshorst, Simon W. Nienhuijs, and Ignace H. de Hingh, "Treatment-Related Mortality After Cytoreductive Surgery and HIPEC in Patients with Colorectal Peritoneal Carcinomatosis is Underestimated by Conventional Parameters", Ann Surg Oncol (2016) 23:99–105, DOI 10.1245/s10434-015-4699-5. (REF 43)

44. Malcolm H. Squires, Christopher A. Staley, William Knechtle, Joshua H. Winer, Maria C. Russell, Sebastian Perez, John F. Sweeney, Shishir K. Maithel, and Charles A. Staley, "Association Between Hospital Finances, Payer Mix, and Complications After Hyperthermic Intraperitoneal Chemotherapy: Deficiencies in the Current Healthcare Reimbursement System and Future Implications", Ann Surg Oncol (2015) 22:1739–1745, DOI 10.1245/s10434-014-4025-7. (REF 44)

45. Winson Jianhong Tan, Joelle Fui Sze Wong, Claramae Shulyn Chia, Grace Hwee Ching Tan, Khee Chee Soo, and Melissa Ching Ching Teo, "Quality of Life After Cytoreductive

Surgery and Hyperthermic Intraperitoneal Chemotherapy: An Asian Perspective", Ann Surg Oncol (2013) 20:4219–4223, DOI 10.1245/s10434-013-3133-0. (REF 45)

46. K. Turaga, E. Levine, R. Barone, R. Sticca, N. Petrelli, L. Lambert, G. Nash, M. Morse, R. Adbel-Misih, H. R. Alexander, F. Attiyeh1, D. Bartlett, A. Bastidas, T. Blazer, Q. Chu, K. Chung, L. Dominguez-Parra, N. J. Espat, J. Foster, K. Fournier, R. Garcia, M. Goodman, N. Hanna, L. Harrison, R. Hoefer, M. Holtzman, J. Kane, D. Labow, B. Li, A. Lowy, P. Mansfield, E. Ong, C. Pameijer, J. Pingpank, M. Quinones, R. Royal, G. Salti, A. Sardi, P. Shen, J. Skitzki, J. Spellman, J. Stewart, and J. Esquivel, "Consensus Guidelines from The American Society of Peritoneal Surface Malignancies on Standardizing the Delivery of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Colorectal Cancer Patients in the United States", Ann Surg Oncol (2014) 21:1501–1505, DOI 10.1245/s10434-013-3061-z. (REF 46)

47. Pietro F. Bagnoli, F.C.M. Cananzi, A. Brocchi, A. Ardito, D. Strada, L. Cozzaglio, C. Mussi, S. Brusa, C. Carlino, B. Borrelli, F. Alemanno, V. Quagliuolo, "Peritonectomy and hyperthermic intraperitoneal chemotherapy: Cost analysis and sustainability", EJSO 41 (2015) 386-391, http://dx.doi.org/10.1016/j.ejso.2014.12.004. (REF 47)

48. L.G.E.M. Razenberg, Y.R.B.M. van Gestel, G.-J. Creemers, V.J. Verwaal, V.E.P.P. Lemmens, I.H.J.T. de Hingh, "Trends in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of synchronous peritoneal carcinomatosis of colorectal origin in the Netherlands", EJSO 41 (2015) 466e471, http://dx.doi.org/10.1016/j.ejso.2015.01.018. (REF 48)

49. D. Baratti, A. Scivales, M.R. Balestra, P. Ponzi, F. Di Stasi, S. Kusamura, B. Laterza, M. Deraco, "Cost analysis of the combined procedure of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)", EJSO 36 (2010) 463e469, doi:10.1016/j.ejso.2010.03.005. (REF 49)

50. G. Ferron, L. Simon, F. Guyon, O. Glehen, D. Goere, D. Elias, M. Pocard, L. Gladieff, J.M. Bereder, C. Brigand, J.M. Classe, J.M. Guilloit , F. Quenet, K. Abboud, C. Arvieux , F. Bibeau, C. De Chaisemartin, D. Delroeux, S. Durand-Fontanier, N. Goasguen, L. Gouthi, B. Heyd, R. Kianmanesh, E. Leblanc, V. Loi, G. Lorimier, F. Marchal, P. Mariani, C. Mariette, P. Meeus, S. Msika, P. Ortega-Deballon, J. Paineau, D. Pezet, G. Piessen, N. Pirro, C. Pomel, J. Porcheron, G. Pourcher, P. Rat, J.M. Regimbeau, C. Sabbagh, E. Thibaudeau, J.J. Torrent, D. Tougeron, J.J. Tuech, F. Zinzindohoue, P. Lundberg, F. Herin, L. Villeneuve, "Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): A French multicentric survey", EJSO 41 (2015) 1361-1367, http://dx.doi.org/10.1016/j.ejso.2015.07.012, (REF 50)

51. S. Kusamura, D. Baratti, I. Hutanu, C. Gavazzi, D. Morelli, D.R. Iusco, A. Grassi, S. Bonomi, S. Virzı , E. Haeusler, M. Deraco, "The role of baseline inflammatory-based scores

and serum tumor markers to risk stratify pseudomyxoma peritonei patients treated with cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)", EJSO 41 (2015) 1097-1105, http://dx.doi.org/10.1016/j.ejso.2015.04.005. (REF 51)

52. A.M. Kuijpers, M. Hauptmann, A.G. Aalbers, S.W. Nienhuijs, I.H. de Hingh, M.J. Wiezer, B. van Ramshorst, R.J. van Ginkel, K. Havenga, V.J. Verwaal, "Cytoreduction and hyperthermic intraperitoneal chemotherapy: The learning curve reassessed", EJSO 42 (2016) 244-250, http://dx.doi.org/10.1016/j.ejso.2015.08.162. (REF 52)

53. Emel Canbay, Haruaki Ishibashi, Shouzou Sako, Akiyoshi Mizumoto, Masamitsu Hirano, Masumi Ichinose, Nobuyuki Takao, Yutaka Yonemura, "Preoperative Carcinoembryonic Antigen Level Predicts Prognosis in Patients with Pseudomyxoma Peritonei Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy", World J Surg (2013) 37:1271–1276, DOI 10.1007/s00268-013-1988-7. (REF 53)

54. Mariangela Desantis, Jean-Louis Bernard, Vincent Casanova, Marianne Cegarra-Escolano, Emmanuel Benizri, Amine M. Rahili, Daniel Benchimol, Jean-Marc Bereder, "Morbidity, mortality, and oncological outcomes of 401 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC)", Langenbecks Arch Surg (2015) 400:37–48, DOI 10.1007/s00423-014-1253-z. (REF 54)

55. Nikolaos Tsilimparis, Christina Bockelmann, Wieland Raue, Charalambos Menenakos, Sebastian Perez, Beate Rau, and Jens Hartmann, "Quality of Life in Patients after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Is It Worth the Risk?", Ann Surg Oncol (2013) 20:226–232, DOI 10.1245/s10434-012-2579-9. (REF 55)

56. Konstantinos Votanopoulos, Chukwuemeka Ihemelandu, Perry Shen, John Stewart, Gregory Russell, and Edward A. Levine, "A comparison of hematologic toxicity profiles after heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C", Journal of surgical research 179 (2013) 133-139, doi:10.1016/j.jss.2012.01.015. (REF 56)

57. J.B. Delhorme, E. Triki, B. Romain, N. Meyer, S. Rohr, C. Brigand, "Routine second-look after surgical treatment of colonic peritoneal carcinomatosis", Journal of Visceral Surgery (2015) 152, 149-154, http://dx.doi.org/10.1016/j.jviscsurg.2015.01.002. (REF 57)

58. N. Bakrin, J.M. Bereder, E. Decullier, J.M. Classe, S. Msika, G. Lorimier, K. Abboud, P. Meeus, G. Ferron, F. Quenet, F. Marchal, S. Gouy, P. Morice, C. Pomel, M. Pocard, F. Guyon, J. Porcheron, O. Glehen, "Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients", EJSO 39 (2013) 1435e1443, http://dx.doi.org/10.1016/j.ejso.2013.09.030. (REF 58)

59. Ioannis Kyriazanos, Vasileios Kalles, Anastasios Stefanopoulos, John Spiliotis, Faheez Mohamed, "Operating personnel safety during the administration of Hyperthermic

Intraperitoneal Chemotherapy (HIPEC)", Surgical Oncology 25 (2016) 308-314, http://dx.doi.org/10.1016/j.suronc.2016.06.001. (REF 59)

60. Lawrence E. Harrison, Greg Tiesi, Reza Razavi, and Chia-Chi Wang, "A Phase I Trial of Thermal Sensitization Using Induced Oxidative Stress in the Context of HIPEC", Ann Surg Oncol (2013) 20:1843–1850, DOI 10.1245/s10434-013-2874-0. (REF 60)

61. Jean Sebastien Frenel, Christophe Leux, Luc Pouplin, Gwenael Ferron, Dominique Berton Rigaud, Emmanuelle Bourbouloux, Francois Dravet, Isabelle Jaffre, And Jean Marc Classe, "Oxaliplatin-Based Hyperthermic Intraperitoneal Chemotherapy in Primary or Recurrent Epithelial Ovarian Cancer: A Pilot Study of 31 Patients", J. Surg. Oncol. 2011;103:10–16, DOI 10.1002/jso.21732. (REF 61)

62. Chao-Qun Huang, Xiao-Jun Yang, Yang Yu, Hai-Tao Wu, Yang Liu, Yutaka Yonemura, Yan Li, "Cytoreductive Surgery plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival for Patients with Peritoneal Carcinomatosis from Colorectal Cancer: A Phase II Study from a Chinese Center", PLOS ONE (2014), Volume 9, Issue 9, e108509. (REF 62)

63. Mark A. Rettenmaier, Alberto A. Mendivil, Lisa N. Abaid, John V. Brown III, Amber M. Wilcox & Bram H. Goldstein, "Consolidation hyperthermic intraperitoneal chemotherapy and maintenance chemotherapy following laparoscopic cytoreductive surgery in the treatment of ovarian carcinoma", International Journal of Hyperthermia (2015), 31:1, 8-14, DOI:10.3109/02656736.2014.991766. (REF 63)

64. Jin-Yu Huang, Ying-Ying Xu, Zhe Sun, Zhi Zhu, Yong-Xi Song, Peng-Tao Guo, Yi You, Hui-Mian Xu, "Comparison Different Methods of Intraoperative and Intraperitoneal Chemotherapy for Patients with Gastric Cancer: A Meta-analysis", Asian Pacific J Cancer Prev, 13 (9), 4379-4385, DOI:http://dx.doi.org/10.7314/APJCP.2012.13.9.4379. (REF 64)

65. Terence C. Chua, Liam E. Quinn, Jing Zhao, And David L. Morris, "Iterative Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Recurrent Peritoneal Metastases", Journal of Surgical Oncology 2013;108:81–88, DOI 10.1002/jso.23356. (REF 65).

66. Osama M Al-Quteimat and Mariam A Al-Badaineh, "Intraperitoneal chemotherapy: Rationale, applications, and limitations", J Oncol Pharm Practice 2014, Vol. 20(5) 369–380, DOI: 10.1177/1078155213506244. (REF 66)

67. Shigeki Kusamura, Dario Baratti, Ionut Hutanu, Piero Rossi, Marcello Deraco, "The Importance of the Learning Curve and Surveillance of Surgical Performance in Peritoneal Surface Malignancy Programs", Surg Oncol Clin N Am 21 (2012) 559–576, http://dx.doi.org/10.1016/j.soc.2012.07.011. (REF 67)

68. Hai-Tao Wu, Xiao-Jun Yang, Chao-Qun Huang, Jian-Hua Sun, Zhong-He Ji, Kai-Wen Peng, Qian Zhang and Yan Li, "Cytoreductive surgery plus hyperthermic intraperitoneal

chemotherapy with lobaplatin and docetaxel improves survival for patients with peritoneal carcinomatosis from abdominal and pelvic malignancies", World Journal of Surgical Oncology (2016) 14:246 DOI 10.1186/s12957-016-1004-4 (REF 68)

69. L. Graziosi, E. Marino, V. De Angelis, A. Rebonato and A. Donini, "Survival prognostic factors in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy treatment: analysis from a single oncological center.", World Journal of Surgical Oncology (2016) 14:97 DOI 10.1186/s12957-016-0856-y (REF 69)

70. Nikolaos Vassos, Thomas Förtsch, Archil Aladashvili, Werner Hohenberger and Roland S. Croner, "Repeated cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with recurrent peritoneal carcinomatosis", World Journal of Surgical Oncology (2016) 14:42 DOI 10.1186/s12957-016-0804-x (REF 70)

71. Yang Liu, Yoshio Endo, Takuji Fujita, Haruaki Ishibashi, Toshihiro Nishioka, Emel Canbay, Yan Li, MD, Shun-ichiro Ogura and Yutaka Yonemura, "Cytoreductive Surgery Under Aminolevulinic Acid-Mediated Photodynamic Diagnosis Plus Hyperthermic Intraperitoneal Chemotherapy in Patients with Peritoneal Carcinomatosis from Ovarian Cancer and Primary Peritoneal Carcinoma: Results of a Phase I Trial", Ann Surg Oncol (2014) 21:4256–4262, DOI 10.1245/s10434-014-3901-5 (REF 71)

72. Wilson L Costa Jr, Felipe J F Coimbra, Héber S C Ribeiro, Alessandro L Diniz, André Luís de Godoy, Maria Dirlei F S Begnami, Milton J B Silva, Marcelo F Fanelli and Celso A L Mello "Safety and preliminary results of perioperative chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) for high-risk gastric cancer patients", World Journal of Surgical Oncology 2012, 10:195, http://www.wjso.com/content/10/1/195 (REF 72)

73. Lilian Schwarz, Konstantinos Votanopoulos, David Morris, Yutaka Yonemura, Marcello Deraco, Pompiliu Piso, Brendan Moran, Edward A. Levine, and Jean-Jacques Tuech, "Is the Combination of Distal Pancreatectomy and Cytoreductive Surgery With HIPEC Reasonable? Results of an International Multicenter Study", (Ann Surg 2016;263:369–375, DOI: 10.1097/SLA.0000000000001225 (REF 73)

74. Rebecca Fish, Chelliah Selvasekar, Peter Crichton, Malcolm Wilson, Paul Fulford, Andrew Renehan, Sarah O'Dwyer "Risk-reducing laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for low-grade appendiceal mucinous neoplasm: early outcomes and technique", Surg Endosc (2014) 28:341–345, DOI 10.1007/s00464-013-3189-8 (REF 74)

75. Ou Huang, XiangHong Lu, XiangDong Xu, Yong Shi "Fibrin-Sealant-Delivered Cisplatin Chemotherapy Versus Cisplatin Hyperthermic Intraperitoneal Perfusion Chemotherapy for Locally Advanced Gastric Cancer Without Peritoneal Metastases: A Randomized Phase-II Clinical Trial with a 40-Month Follow-up", Cell Biochem Biophys (2015) 71:1171–1180

DOI 10.1007/s12013-014-0326-5 (REF 75)

76. Jehan M. Kamal, Somaya M. Elshaikh, Dina Nabil, Ahmad M. Mohamad "The perioperative course and anesthetic challenge for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy", Egyptian Journal of Anaesthesia (2013) 29, 311–318 (REF 76)

77. Parissa Tabrizian, Ghalib Jibara, Brian Shrager, Bernardo Franssen, Ming-Jim Yang, Umut Sarpel, Spiros Hiotis, Daniel Labow "Outcomes for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the elderly", Surgical Oncology 22 (2013) 184e189 (REF 77)

78. Wim P. Ceelen, Marc Peeters, Philippe Houtmeyers, Christophe Breusegem, Filip De Somer and Piet Pattyn, "Safety and Efficacy of Hyperthermic Intraperitoneal Chemoperfusion with High-Dose Oxaliplatin in Patients with Peritoneal Carcinomatosis", Annals of Surgical Oncology 15(2):535–541 DOI: 10.1245/s10434-007-9648-5 (REF 78)

79. Xiao-Jun Yang, Yan Li MD, Alaa Hammed al-shammaa Hassan, Guo-Liang Yang, Shao-Yang Liu, Yu-Lan Lu, Jing-Wei Zhang, and Yukata Yonemura "Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival in Selected Patients with Peritoneal Carcinomatosis from Abdominal and Pelvic Malignancies: Results of 21 Cases", Ann Surg Oncol (2009) 16:345–351, DOI 10.1245/s10434-008-0226-2 (REF 79)

80. Yang Liu, Haruaki Ishibashi, Kazuyoshi Takeshita, Akiyoshi Mizumoto, Masamitsu Hirano, Shouzou Sako, Shigeru Takegawa, Nobuyuki Takao, Masumi Ichinose, and Yutaka Yonemura, "Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Dissemination from Small Bowel Malignancy: Results from a Single Specialized Center", Ann Surg Oncol (2016) 23:1625–1631, DOI 10.1245/s10434-015-5056-4 (REF 80)

81. Jesus Esquivel, Andrew Averbach, and Terence C. Chua "Laparoscopic Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Patients with Limited Peritoneal Surface Malignancies Feasibility, Morbidity and Outcome in an Early Experience", Ann Surg 2011;253:764–768, DOI: 10.1097/SLA.0b013e31820784df (REF 81)

82. Patricio M. Polanco, Ying Ding, Jordan M. Knox, Lekshmi Ramalingam, Heather Jones, Melissa E. Hogg, Amer H. Zureikat, Matthew P. Holtzman, James Pingpank, Steven Ahrendt, Herbert J. Zeh, David L. Bartlett, and Haroon A. Choudry, "Outcomes of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemoperfusion in Patients with High-Grade, High-Volume Disseminated Mucinous Appendiceal Neoplasms" Ann Surg Oncol (2016) 23:382–390, DOI 10.1245/s10434-015-4838-z, (REF 82)

83. Fernando Arias, Gabriel Herrera-Almario, Marcos E. Pozo, Eduardo London˜oSchimmer, Jorge M. Otero, Andres Cardona, Natalia Cortes, andMarta Mora, "Safety and Quality Outcomes in Peritoneal Surface Malignancy Patients: Developing a National Center for Excellence in Colombia", Ann Surg Oncol (2015) 22:1733–1738, DOI 10.1245/s10434-014-4064-0 (REF 83)

84. Anke M. J. Kuijpers, Boj Mirck, Arend G. J. Aalbers, Simon W. Nienhuijs, Ignace H. J. T. de Hingh, Martinus J. Wiezer, Bert van Ramshorst, Robert J. Van Ginkel, Klaas Havenga, Andreas J. Bremers, Johannes H. W. de Wilt, Elisabeth A. te Velde, and Vic J. Verwaal, "Cytoreduction and HIPEC in The Netherlands: Nationwide Long-term Outcome Following the Dutch Protocol", Ann Surg Oncol (2013) 20:4224–4230, DOI 10.1245/s10434-013-3145-9 (REF 84)

85. Daphne Hompes, Andre´ D'Hoore, Eric Van Cutsem, Steffen Fieuws, Wim Ceelen, Marc Peeters, Kurt Van der Speeten, Claude Bertrand, Hugues Legendre, and Joseph Kerger, "The Treatment of Peritoneal Carcinomatosis of Colorectal Cancer with Complete Cytoreductive Surgery and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) with Oxaliplatin: A Belgian Multicentre Prospective Phase II Clinical Study", Ann Surg Oncol (2012) 19:2186–2194, DOI 10.1245/s10434-012-2264-z (REF 85)

86. Xiao-Jun Yang, Chao-Qun Huang, Tao Suo, Lie-Jun Mei, Guo-Liang Yang, Fu-Lin Cheng, Yun-Feng Zhou, Bin Xiong, Yutaka Yonemura, and Yan Li, "Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial", Ann Surg Oncol (2011) 18:1575–1581, DOI 10.1245/s10434-011-1631-5, (REF 86)

87. Lawrence E. Harrison, Margarette Bryan, Lilian Pliner, and Tracie Saunders, "Phase I Trial of Pegylated Liposomal Doxorubicin with Hyperthermic Intraperitoneal Chemotherapy in Patients Undergoing Cytoreduction for Advanced Intra-abdominal Malignancy", Annals of Surgical Oncology 15(5):1407–1413, DOI: 10.1245/s10434-007-9718-8 (REF 87)

88. L. Benhaim, C. Honore, D. Goere, J.-B. Delhorme, D. Elias, "Huge pseudomyxoma peritonei: Surgical strategies and procedures to employ to optimize the rate of complete cytoreductive surgery", EJSO 42 (2016) 552e557, http://dx.doi.org/10.1016/j.ejso.2016.01.015 (REF 88)

89. T. Shimizu, H. Sonoda, S. Murata, K. Takebayashi, H. Ohta, T. Miyake, E. Mekata, H. Shiomi, S. Naka, T. Tani, "Hyperthermic intraperitoneal chemotherapy using a combination of mitomycin C,5-fluorouracil, and oxaliplatin in patients at high risk of colorectal peritoneal metastasis: A Phase I clinical study", EJSO 40 (2014) 521e528, http://dx.doi.org/10.1016/j.ejso.2013.12.005 (REF 89)

90. G. Passot, N. Bakrin, S. Isaac, E. Decullier, F.N. Gilly, O. Glehen, E. Cotte, "Postoperative outcomes of laparoscopic vs open cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of peritoneal surface malignancies", EJSO 40 (2014) 957e962, http://dx.doi.org/10.1016/j.ejso.2013.10.002 (REF 90)

91. Yan Li, Yun-Feng Zhou, Han Liang, Hua-Qing Wang, Ji-Hui Hao, Zheng-Gang Zhu, De-Seng Wan, Lun-Xiu Qin, Shu-Zhong Cui, Jia-Fu Ji, Hui-Mian Xu, Shao-Zhong Wei, Hong-Bin Xu, Tao Suo, Shu-Jun Yang, Cong-Hua Xie, Xiao-Jun Yang, Guo-Liang Yang, "Chinese

expert consensus on cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal malignancies", World J Gastroenterol 2016 August 14; 22(30): 6906-6916, DOI: 10.3748/wjg.v22.i30.6906 (REF 91)

92. John C. Bell, Barnaby G. Rylah, Robert W. Chambers, Helen Peet, Faheez Mohamed, " and Brendan J. Moran, "Perioperative Management of Patients Undergoing Cytoreductive Surgery Combined with Heated Intraperitoneal Chemotherapy for Peritoneal Surface Malignancy: A Multi-Institutional Experience", Ann Surg Oncol (2012) 19:4244–4251, DOI 10.1245/s10434-012-2496-y (REF 92)

93. Naciye Çigdem Arslan, Selman Sökmen, Vildan Avkan Oguz, Gülsen Atasoy, Tayfun Bişgin, Aras Emre Canda, Cem Terzi, Mehmet Fuzun, "Kolorektal Kanser Kökenli Peritoneal Karsinomatoz Tedavisinde Enfeksiyöz Komplikaslar ve Risk Faktörler", Kolon Rektum Hast Derg 2015;25:122-130, (REF 93)

94. Cem Terzi, Uğur Yılmaz, Can Yakut, Mücahit Özbilgin, Funda Obuz, Sülen Sarıoğlu, Mehmet Füzün, "Kolorektal kanser kaynaklı peritoneal karsinomatozis olgusunda sitoredüksiyon ve hipertermik intraperitoneal kemoterapi uygulamasý ve literatürün gözden geçirilmesi", Ulusal Cerrahi Dergisi YIL//2008 CİLT//24 SAYI//1 OCAK-ŞUBAT-MART (REF 94)

95. Naciye Cigdem Arslan, Selman Sokmen, Vildan Avkan-Oguz, Funda Obuz, Aras Emre Canda, Cem Terzi, and Mehmet Fuzun, "Infectious Complications after Cytoreductive Surgery and Hyperthermic Intra-Peritoneal Chemotherapy", SURGICAL INFECTIONS Volume 18, Number 2, 2017, DOI: 10.1089/sur.2016.102 (REF 95)

96. Kürşat Karadayi, Mustafa Turan, Şule Karadayi, Hakan Alagözlü, Saadettin Kiliçkap, Abdullah Büyükçelik, Cihat Şarkiş, Birsen Yücel, Abdullah Boztosun, Meral Çetin, Abdulkerim Yilmaz, Ali Yanik, Metin Şen, "Cytoreductive Surgery Followed By Hyperthermic Intraperitoneal Chemotherapy: Morbidity And Mortality Analysis Of Our Patients", Tuiye Klinikleri J Med Sci 2012;32(1):162-70, doi: 10.5336/medsci.2011-23538 (REF 96)

97. Koray Topgül, Mehmet Bilge Çetinkaya, N. Çiğdem Arslan, Mustafa Kemal Gül, Murat Çan, Mahmut Fikret Gürsel, Dilek Erdem, Zafer Malazgirt, "Cytoreductive surgery (SRC) and hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal carcinomatosis: Our initial experience and technical details", Ulus Cerrahi Derg 2015; 31: 138-147, DOI: 10.5152/UCD.2015.2990 (REF 97)

98. Nagarajan P, Renehan A, Saunders MP, Wilson MS, O'Dwyer ST, "Sugarbaker procedure for pseudomyxoma peritonei (Protocol)", Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005659., DOI: 10.1002/14651858.CD005659. (REF 98)

99. Verzijden JCM, Klaver YLB, de Hingh IHJT, Bleichrodt RP, "Cytoreductive surgery

and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis in patients with colorectal cancer (Protocol)", Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD008479., DOI: 10.1002/14651858.CD008479 (REF 99)

100. Betül Güven Aytaç, İsmail Aytaç, Semih Başkan, "Sitoredüktif Cerrahi ile Kombine Hipertermik İntraperitoneal Kemoterapi Uygulamalarında Anestezi Yönetimi", Acta Oncologica Turcica Cilt: 45 Sayı: 1 – 2012, DOI: 10.5505/aot.2012.98608, (REF 100)

101. Yonca Yanlı, Erdem Akçay, Cafer Yürük, Nurten Bakan, "Hipertermik kemoterapi uygulanan apandis tümörü hastasında anestezik yaklaşım", Journal of Clinical and Experimental Investigations 2013; 4 (2): 234-237, doi: 10.5799/ahinjs.01.2013.02.0274 (REF 101)

102. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, Giassas S. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5 (REF 102)

ANNEX 2: Conflict of Interest Statement (Declaration of Neutrality) form

DECLARATION OF NEUTRALITY (CONFLICT OF INTEREST STATEMENT) FORM

As to the subject matter of HTA during the process of the Health Technology Assessment (HTA) study on **"Hipertermic Intraperitoneal Chemotherapy (HIPEC)"**, the following should be clearly indicated and signed:

1. During the assessment process of the study, whether or not any moral and material support that will adversely affect the decision related to the study is taken from a natural or legal person who produces, imports, distributes and/or provides any directly or indirectly related drug, medical device or the other products,

2. Whether or not there is there is a scientific and / or medical committee membership or consultancy, expertness, actual employment status, shareholding and the like, which have a potential for conflict of interest,

3. Whether or not there is any relationship based on self-interest for collecting data, interpreting the results, and writing HTA report.

☐ There is NO potential for financial contribution, relationship based on self-interest or other conflict of interest that should be known with regard to the objectivity of our article/our contribution to HTA report.

……..	……..	……
Name-Surname	Date	Signature

☐ There IS a potential for financial contribution, relationship based on self-interest or other conflict of interest that should be known with regard to the objectivity of our article/our contribution to HTA report*. (*Please explain that kind of relationship based on self-interest that may negatively affect your objectivity).

…….....

…….....

……..……..	……..	……
Name-Surname	Date	Signature