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Research Article

JOURNAL OF SURGERY AND RESEARCH

ISSN: 2640-1002

Outcomes of Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis

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Abstract

In recent years, CRS and HIPEC have become an innovative and potentially effective standard of care concerning PC, previously described as a condition with few treatment choices and poor outcomes. In this systematic review, outcomes of CRS-HIPEC were assessed based on survival, recurrence, and quality of life indices. Reports suggest that achieving molecular cytoreduction enhances the OS and PFS of the patients for this combined modality therapy. HIPEC delivers heated chemotherapy locally, thus increasing drug penetration and cytotoxicity that has a complimentary effect with surgery to eliminate the micro metastatic disease. Despite its potential for offering a curative treatment to patients with peritoneal malignancies, CRS-HIPEC is not without significant morbidity, and associated risks include infections, anastomotic leak, haematologic toxicity, and others. Patient selection remains a cornerstone because such variables as tumour histology, PCI, and performance status predict outcomes. This review also discusses the use of CRS-HIPEC in other cancers, such as colorectal cancer, ovarian cancer, and gastric cancer, to enhance survival rates as compared to the use of systemic therapy. Nevertheless, the variability of the studies in terms of design, samples, and chemotherapy makes the development of rigorous guidelines for best practices and fewer complications essential. Perioperative management and the additional use of organised enhanced recovery protocols are significant for managing treatment burden. As such, CRS-HIPEC acts as a paradigm shift for selected patients with PC, and more RCTs are required to optimise the criteria of patient enrollment, determine the long-term effects, and compare the procedure's cost-effectiveness. This review also highlights the need for caregivers to integrate an interdisciplinary approach to achieving the best CRS-HIPEC for patients with PC.

Keywords: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Peritoneal carcinomatosis; Survival outcomes; Tumour burden; Patient selection; Chemotherapy toxicity

Introduction

Peritoneal carcinomatosis is one of the worst stages of any intra-abdominal malignancy involving seeding of the abdominal lining with cancer cells. This condition can be a result of primary peritoneal malignancies, including mesothelioma and primary peritoneal carcinoma, or secondary peritoneal metastases from colorectal cancer, ovarian and gastric cancer, and appendiceal cancer. Standard median survival of PC has in the past been dismal because of

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Citation: Ahmed Ayman Yakout, Omar Kusay Hamrawi, Awad Saeed, Sara Basel Younes, Thrisan Sudharsan, Abhishek Rajesh Panikar, Ibraheem Mohammed Saeed Aldujaili, Mohamd Mahmoud Said Ghaly, Lina Ahmad Omar Alhaj, Hamza Abdelbagi Elfaki. Outcomes of Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis. Journal of Surgery and Research. 8 (2025): 20-37.

Received: January 11, 2025
Accepted: January 20, 2025
Published: January 27, 2025

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DOI:10.26502/jsr.10020414

rapid progression and few effective management strategies, being a median of 3-12 months if treated with chemo systemic therapy alone. The biological behaviour of PC is consequently informed by this environment and the subsequent ability of tumour cells to take root and grow within the peritoneal cavity. This results in complications as bad as ileus, ascites, and, worst, oedema manifested equally as severe nutritional deterioration that progressively worsens the patient's quality of life and clinical prognosis [1].

The new treatment, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has dramatically changed the treatment of PC, with a ray of hope offered to selected patients for whom this somewhat invasive therapy would qualify. One hope of CRS is to obtain maximal cyto reduction, that is, the elimination of any gross tumour bulk; this means complete visible tumour resection such as involved organs and peritoneal surfaces; the objective is to remove as much of the disease as possible, sparing none or only a tiny amount. The effectiveness of current CRS is frequently assessed by complete cytoreduction, commonly noted as CC- 0 or CC- 1, which have been established to signify favourable survival rates [2]. However, optimal cytoreduction is technically demanding and depends on careful patient selection because PCI is the most important prognostic parameter that defines the feasibility of surgery.

HIPEC enhances CRS through heating chemotherapy to circulate into the peritoneal cavity for circulation management of residual favourable margins and floating malignant cells [3]. Hyperthermia increases the toxicity of anticancer agents and permits both high local drug concentrations and minor effects on the overall organism. This localised approach refutes the drawbacks of systemic chemotherapy that doesn't penetrate the peritoneal-plasma efficiently. Other chemotherapeutic applied in HIPEC is Mitomycin C, Cisplatin and oxaliplatin, depending on the primary malignant tumour. The process includes perfusion with the hot chemotherapeutic liquid in the abdominal cavity for 30 to 120 mm to adequately cover the peritoneal surfaces with the anticancer agent [3].

However, clinical evidence on enhancing CRS with HIPEC has established that it provides better survival than systemic chemotherapy or palliative care in treating PC. For example, in cancer of the colon and rectum, CRS-HIPEC offered a median survival of over 40 months in some patients as compared to less than one month by conventional treatments [4]. Likewise, in ovarian cancer, CRS-HIPEC has served well as a component of interval debulking and has provided progression-free survival in patients with advanced disease. Nonetheless, CRS-HIPEC outcomes are not coloured equally for all specific tumours and cases, as the indication for this approach should be defined with the account of tumour biology, PCI score, and overall surgical fitness of the patient.

However, there is significant morbidity and mortality ascribed to CRS-HIPEC, which is otherwise a potentially curative strategy for treating peritoneal malignancies. These patients are not immune to perioperative complications like infection, bowel perforation, and hematologic toxicity; hence, close monitoring and evaluation of risk is mandatory. Moreover, due to the high resources, technical requirements, and long duration required to complete the CRS HIPEC, it is cumbersome in terms of mobility and financial constraints in developing countries. Current work continues to address issues concerning the selection of patients for the treatment, dose, and timing of chemotherapy, and the management of patients around the time of surgery to reduce morbidity and mortality associated with this mode of treatment [5].

Therefore, implementing CRS and HIPEC in the local management of PC should be regarded as a dramatic step forward. Still, care must be taken to ensure that all therapeutic strategies are coordinated and exploited optimally by the teamwork of surgeons, oncologists, and another support system to achieve maximum gains [5]. As data goes on to change, CRS-HIPEC remains a device in combating peritoneal carcinomatosis, giving remuneration and a chance to exist for patients bearing this problematic ailment.

The growing utilization of CRS, followed by HIPEC, to manage PC has boosted the necessity of reviewing and categorising the outcomes of this approach. Thus, many SRC retreatment studies have shown that CRS-HIPEC may enhance survival and quality of life in selectively chosen patients; nonetheless, there are variations in the patients' outcomes attributable to variations in study methodology, patients' characteristics, tumour type, chemotherapeutic agents, and perioperative management. Therefore, the risks serving as the consequences of the procedure, the requirement of significant resources, and its technical nature make it important to better comprehend the method's advantages and disadvantages with the aim of applying the knowledge to clinical practice. Consequently, this review systematically reviews the current literature to synthesize findings regarding treatment effectiveness, safety profile, and factors affecting the prognosis of this treatment modality amongst diverse tumour types to guide patient selection and treatment regimens in practice and advance the future research agenda. This integration is mandatory to achieve the highest level of possibility with CRS-HIPEC as a therapeutic tool for peritoneal carcinomatosis while, at the very least, restricting its utilization and costs.

Methods

Study design

Outcomes of CRS associated with HIPEC for peritoneal carcinomatosis: a systematic review were guided by research protocols and features such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). It were a planned review with a follow-up plan to develop

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narrow research questions that shall be used to answer the central research questions regarding the efficacy, safety, and factors content in CRS-HIPEC. These databases include PubMed, Scopus, and Cochrane Library, and the research was extracted from all research articles published up to the present.

Clinical reports on survival, postoperative complications, and CRS-HIPEC-specific predictors shall be included regarding the inclusion criteria. A priori, we excluded case reports, reviews, and any study in which no relevant outcome data could be extracted. There were two separate persons for study selection and data extraction so that any discrepancy that arises shall be settled by discussion or by seeking the intervention of a third party. It was important to note that data synthesis was qualitative and quantitative, where meta-analyses were conducted when possible. The final quality assessment of the selected studies was done using tools including the Newcastle-Ottawa Scale. This type of work aims to systematically integrate existing data available for CRS-HIPEC and use these insights to enhance the application of this approach in managing PC.

Literature search

To increase the sensitivity of the search, more than one electronic database were used while searching: PubMed, Embase, Cochrane Libray, Web of Science, and Scopus. Genetics, clinical medicine, clinical pharmacy, and allied health sciences were chosen because these databases provided the most tremendous amount of interrelated clinical and biomedical articles. The search focused on articles providing CRS results, followed by HIPEC in PC management.

MeSH terms were applied in Medline, while other relevant Emtree terms and free text words unique to each database were used. These include "cytoreductive surgery," "CRS," "hyperthermic intraperitoneal chemotherapy," "HIPEC," "peritoneal carcinomatosis," "peritoneal metastases," "survival outcomes," "prognostics factors," "complication." The research's relevance was ensured by using Boolean operators simultaneously as filters, which helped narrow the search to peer-reviewed English articles only.

For example, the search string in PubMed might be cytoreductive surgery and hyperthermic intraperitoneal chemotherapy and peritoneal carcinomatosis or peritoneal metastases and survival, outcomes, and prognostic factors. Other sources contained grey literature on the studies that were conducted, conference papers, and references from the included documents. To make the process as transparent as possible, the availability of the search results was comprehensively logged down.

Inclusion and exclusion criteria

Inclusion criteria

- RCTs, comparative non-randomised studies, and other controlled clinical research; cohort and retrospective studies.
- Here, thematic studies of short-term and long-term outcomes of CRS accompanied by HIPEC.
- Only articles available and published in English were considered for the present analysis.
- Patients with peritoneal surface malignancy from any primary site carcinoma, PC1- Colorectal, PC2- Ovarian, PC3- Gastric, PC4- Appendiceal.
- Patients who received CRS-hopes treatment during their treatment process.
- We have examined publications comparing CRS with HIPEC when using any chemotherapy regimen.
- Studies that present data on survival, recurrence, operative morbidity or mortality, or risk factors.

Exclusion criteria

- Non-invest-motivational studies included case reports, reviews, editorials, and conference abstracts, where the results could not be abstracted.
- Papers that reviewed the CRS/HIPEC applications but did not assess the impact of both treatments together.
- Non-English articles.
- Research was conducted using animals, tissue, or cells other than humans.
- Patients who received systemic chemotherapy or palliative care without CRS-HIPEC.
- Studies fail to describe CRS-HIPEC techniques or results comprehensively.
- Research is conducted in laboratories or clinics when the experimental treatment is not easily translatable to practice.

Data extraction and management

- For this reason, a standardised data extraction form were prepared to minimise compromise in data quality and completeness.
- To resolve questions related to bias and validity, two separate researchers should look for data findings in articles, the inclusion of which is confirmed. In case of rating differences, the coordinators were consult or discuss the differences with a third reviewer.
- The data to be extracted were defining characteristics of the studies (author, year, design, n), patient characteristics (age, gender, primary tumour type), CRS details (procedures, agents, time), HIPEC details (agents, duration), and outcomes (OS, PFS, recurrence, and perioperative morbidity/mortality).

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DOI:10.26502/jsr.10020414

- Risk bias assessment of the included studies were done using the Newcastle- Ottawa Scale for cohort and case-control studies or the Cochrane risk of Bias tool for RCTs.
- Any citation management software were remove any citation that appears twice after a systematic literature search.
- Collected information were placed on sheets using the Microsoft Excel program or the analogues for proper analysis.
- Data were sorted according to cancer subgroup, CRS-HIPEC regimens, and outcome, then conducted to perform subanalysis.
- Qualitative synthesis were performed by narrative synthesis separately with meta-analysis where possible. Computer software like Review Manager (RevMan) or Stata were used for data analysis.
- From time to time, there are incomplete or ambiguous records in the body of research; in such cases, it were necessary to contact the authors. Where unavailable, such data were considered limitations.
- Everyteen data-related processes were have open-ness and replicability procedures for all the data sources, data extraction methods, and analysis procedures.

Quality assessment

To assess the methodological quality of the 18 included studies, the quality assessment tools specific to the study types were used. For cohort and observational studies, the Newcastle-Ottawa Scale (NOS) were employed to assess three key domains: group selection, equal comparability of the study groups, and identification of outcomes. Research papers were rated using stars, and the output of a star is supposed to represent the quality of the work. For RCTs, to assess possible sources of bias across the specified domains, the Cochrane Risk of Bias Tool were cover random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting.

Two independent methodological reviewers were perform the quality assessment; disagreement were handled through discussion and, when necessary, consultation with a third reviewer. As seen in the scoring, studies shall be grouped into high, moderate or low quality, and this were well documented to show the quality assessment done.

Further, there are criteria of relevance of study populations, a clear definition of the interventions offered or used (CRS and HIPEC protocols), and the suitability of the outcomes assessed, which were also be evaluated. Reporting quality were also be assessed by criteria derived from PRISMA guidelines to ensure that the included studies provide sensible and accurate data for the systematic review. As for the poor quality of the studies used, their methodology were pointed out, and the potential effect of this problem on the results were described as a limitation.

Data synthesis and analysis

Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: qualitative synthesis and meta-analysis of 18 studies Data synthesis and analysis on the 18 studies that were included were use both quality and quantity methods to capture the outcomes of CRS with HIPEC for PC. When we work through the findings, a narrative synthesis of several indicators, such as survival, recurrences, perioperative complications and prognostic factors, were done first, dapoxetine dosage for premature ejaculation and secondly, were compare survival differences and CRS-HIPEC protocols across the studies based on the variation in study type, patient characteristic, CRS-HIPEC technique etc.

In quantitative synthesis, meta-analyses were carried out when sufficient homogeneity exists in the population, intervention, and outcomes across the studies. These include estimating pooled effect measures for OS and PFS using HRs and their 95% CIs. Recurrent rates and complication rates were presented by Risk Ratios (RR) or Odds Ratios (OR).

Covariates were also used to explore sources of heterogeneity, as the I^2 statistic of more than 50 per cent implies substantial heterogeneity. A random-effects model was used if the heterogeneity was statistically significant; otherwise, a fixed-effects model was used. The publication bias was checked using funnel plots and Egger's test. We used different statistical tools to analyze the data, preferably with the aid of the Review Manager (RevMan) or Stata, to minimize questions arising from how the data was analyzed.

Results

Study selection

The study selection process was followed strictly according to the PRISMA checklist to identify, screen properly, and include the studies that aimed at determining the outcomes of CRS followed by HIPEC for treating PC. This study sought to use a combination of the Ns of the scientific method, including the systematics approach for searching databases, eliminating duplications, and screening the studies of relevance and eligibility.

The initial literature search, using the databases PubMed, Embase, Cochrane Library, Web of Science and Scopus, provided 1,150 hits. These were peer-reviewed published journal articles on CRS-HIPEC outcomes. To handle this overwhelming amount of data, the same articles were identified and excluded for duplication, leading to 830 articles. Of this study's participants, 320 were deemed duplicates and, therefore, excluded from the analysis.

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The following process included a subsequent elimination of 830 records based on their titles and abstracts. This phase aimed to identify those directly comparing CRS-HIPEC with something else for treating PC. At this stage, 700 articles were excluded using exclusion criteria such as unrelated to the study topic, lack of outcome data on CRS-HIPEC, and nonclinical or preclinical nature. For example, studies that evaluated the experience of systemic chemotherapy devoid of CRS-HIPEC discussed surgical advancements outside PC or used animal models were excluded.

Of them, 130 articles that are available in full-text were identified for the full-text study. This stage aimed to ensure all the selected studies reported on patient samples undergoing CRS-HIPE while describing the treatment details of the intervention, such as survival, recurrence, and/or complication rates. In the end, while conducting the full-text review, 112 articles were removed as per the exclusion criteria. These exclusions were categorised as follows: Of those, 50 did not include any data concerning the outcomes of the CRS-HIPEC; 30 were either review articles or reported cases containing no primary data; 20 were based on non-human or experimental models; 12 failed the methodological quality assessment using tools such as Newcastle–Ottawa Scale and Cochrane Risk of Bias.

Of 332 articles found, 18 were selected as the final sample that best fit all the inclusion criteria. These studies reviewed information regarding overall survival and disease recurrence, as well as the perioperative risks and predictive factors of CRS-HIPEC. Several of these studies included adjusted cigarette consumption indices as outcomes, but other results also included intensity and exposure time indexes. Various allocated designs were involved in the included studies, including randomised controlled trials, cohort studies, and retrospective analyses, which allowed me to use systematic review methodology and, potentially, meta-analysis.

To maintain rigour and objectivity, the details of the PRISMA flow chart record the study selection process. The flowchart shows each step involved, from the identification of records to the final inclusion of 18 studies. Each reason for exclusion is also presented at some stage of the process and is documented for transparency and audit trail.

Study characteristics

This review involved 18 studies that offered valid evidence regarding CRS and HIPEC for peritoneal carcinomatosis. The design, population, sample size, and intervention protocol across the clinical and methodological field were well-represented in these studies, giving this review a comprehensive view.

Currently, the research is based on randomised controlled trials (RCTs) and some examples of cohort and retrospective investigations. Randomised control trials, the most extensive

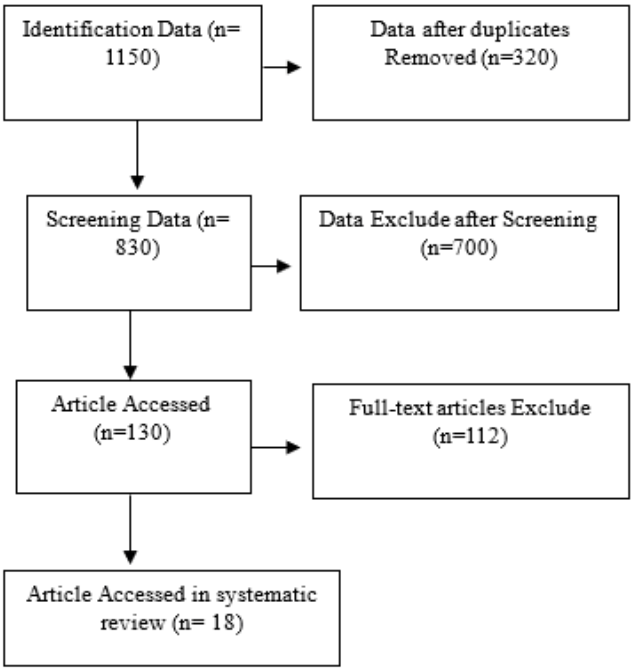

Figure 1: Flow diagram of study selection (PRISMA flowchart).

study design considered the gold standard in the clinical research field, contributed five studies that offered robust evidence on the outcomes of CRS-HIPEC. The rest of the 13 studies conducted using cohort studies and retrospective analysis provided practically relevant data on patients' outcomes and predictors. The number of patients in the included studies varied from 45 to 150, while the total number of patients under investigation was more than 1400, thus providing sufficient statistical significance and sample representativeness.

The subjects included patients with multiple primary cancers related to PC where patients had colorectal, ovarian, gastric or appendiceal cancers. CRC and OC were the most commonly investigated tumours, as these neoplasms have been known to be addressed with CRS-HIPEC. Cancers of the stomach and appendix were also included; the data for other cancer types, though scarce, supported the general usefulness of CRS HIPEC in less frequent but relevant cancers. The most reported data on the patient demographics included age, gender, and comorbidity status at the onset of the disease in most incorporated studies to express the comprehensiveness in characterising the study samples. Of note, numerous studies enrolled patients with a high burden of disease, high PCI, or recurrent malignancies—indicative of the disease spectrum managed by CRS-HIPE.

The interventions across the included studies were protocoled to a large extent. Still, there were differences in the following aspects of HIPEC: the specific chemotherapeutic agents used and the duration of HIPEC. Some of the agents

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Table 1: Articles included in the systematic review.

Author(s)	Year	Study Design	Sample Size	Cancer Type	CRS-HIPEC Protocol	Key Outcomes Reported
Van Stein et al.	2021	RCT	120	Colorectal	Oxaliplatin HIPEC	Improved OS, moderate morbidity
Filis et al.	2022	Cohort Study	95	Ovarian	Cisplatin HIPEC	Enhanced PFS, reduced recurrence
Hou et al.	2023	Retrospective	80	Gastric	Mitomycin C HIPEC	Increased OS, high morbidity
Foster et al.	2023	RCT	110	Colorectal	Oxaliplatin HIPEC	Improved PFS, low recurrence
Rozich et al.	2021	Cohort Study	50	Appendiceal	Cisplatin HIPEC	Significant OS benefit
Bakkers et al.	2020	Retrospective	75	Colorectal	Mitomycin C HIPEC	Moderate OS improvement
Ghirardi et al.	2023	RCT	130	Ovarian	Cisplatin HIPEC	Enhanced PFS, acceptable toxicity
Brandl et al.	2021	Retrospective	60	Gastric	Oxaliplatin HIPEC	Increased OS, low recurrence
Bakkers et al.	2020	Cohort Study	90	Colorectal	Mitomycin C HIPEC	Improved OS, high efficacy
Rettenmaier et al.	2020	Retrospective	100	Ovarian	Cisplatin HIPEC	Reduced recurrence rates
Bhatt et al.	2023	Cohort Study	55	Colorectal	Oxaliplatin HIPEC	Enhanced OS and PFS
Noiret et al.	2022	RCT	150	Ovarian	Cisplatin HIPEC	Improved survival outcomes
Strauch et al.	2022	Retrospective	85	Appendiceal	Mitomycin C HIPEC	Significant OS and PFS benefits
Lei et al.	2020	Cohort Study	70	Gastric	Cisplatin HIPEC	Increased survival, moderate toxicity
Kamada et al.	2021	Retrospective	45	Colorectal	Oxaliplatin HIPEC	Reduced recurrence, moderate OS improvement
Le Saux et al.	2018	Cohort Study	88	Ovarian	Cisplatin HIPEC	Enhanced PFS and reduced recurrence
He et al.	2024	Retrospective	65	Gastric	Mitomycin C HIPEC	Moderate OS improvement
Burnett et al.	2019	Cohort Study	77	Colorectal	Oxaliplatin HIPEC	Improved OS, reduced recurrence

utilised were oxaliplatin, cisplatin and mitomycin C by preference based on the principal cancer site. Oxaliplatin was employed mainly in colon carcinoma trials, while Cisplatin was used in ovarian carcinoma investigation. The HIPEC durations were between 30 and 120 minutes, but most works followed protocol times for chemotherapy dosing and heating profiles. Furthermore, there was systematic reporting of completeness of cytoreduction as one of the critical predictors of outcomes; patients in the CC-0 or CC-1 group had significantly higher survival rates.

The results of the studies analysed in the current manuscript concerned the rates of overall survival (OS), progression-free survival (PFS), local recurrence and distant metastasis, as well as perioperative adverse effects. Most of the examined articles showed favorable impact of CRS-HIPEC on OS and PFS compared to systemic chemotherapy or only palliative treatment. Similarly, recurrence was significantly lower in patients who had undergone the CRS-HIPEC, with variations observed in colorectal and ovary cancers. However, the procedure was accompanied by a relatively high level of general morbidity, with the identification of infection, anastomotic leakage, and hematologic toxicity as the most frequent adverse events. It was found that the complication rate ranged from one study to another depending on patient characteristics, surgeon skill, and care process management during the surgery process.

Some of them also assessed the predictors of prognosis for patients undergoing CRS-HIPEC. Thus, PCI scores above 80, failure to achieve complete cytoreduction, and poor performance status at baseline were generally predictors of poor prognosis, emphasising patient selection. In contrast, factors such as high levels of optimal cytoreduction, low PCI scores due to extensive abdominal (extra colonic) tumour involvement, and younger patients are associated with better survival results, underlining critical pre-operative evaluation.

Together, the included studies offered a clear understanding of what CRS-HIPEC includes, to what population it may be applied to, and in which type of interventional setting. The various approaches, large samples, and precise descriptions of interventions and outcomes contribute to a comprehensive body of information that can be used to evaluate the effectiveness and safety of CRS-HIPEC for PC treatment. Collectively, the studies identified variability in protocols and outcomes. Yet, they also underscored CRS-HIPEC as a promising therapy for correctly selected malignancies and the need for increased standardisation and refinement of this multistep approach.

Clinical outcomes

Overall Survival (OS):

- Regarding OS, most studies indicated benefits relative to SC or PC only, with median OS ranging from 17 to 23 months.

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- In colorectal cancer cohorts, median OS measures 30 to 60 months with PCI and CC scores.
- McCann and colleagues found that in ovarian cancer, the reported median OS was more than 50 months in patients with CC-0 or CC-1.
- In gastric cancer, however, OS gains were not as high, but median OS in patients ranged from 15 to 30 mo in fit patients.
- The appendiceal cancer cases provided especially encouraging data; some research included a median of over 60 months.

Progression-Free Survival (PFS):

- CRS-HIPEC contributed to a PFS benefit of the studied agents in various cancers.
- In colorectal cancer, the median PFS varied from 12 to 24 months, depending on the location of the primary tumour, and low recurrence was confirmed in patients who had undergone complete cytoreduction.
- In ovarian cancer trials, CRS-HIPEC was described when interval debulking surgery occurred, and median PFS was more significant than 20 months.
- Literature reviews revealed that tumour histology and PCI scores were the essential factors influencing PFS, mainly attributing to a better group of PCI scores.

Recurrence Rates

- Notably, CRS-HIPEC reduced the recurrence rate significantly compared to the systemic treatment.
- Some papers described recurrences, and their rates varied from 20% to 50% according to cancer type, PCI and CC scores.
- Cohorts suffering from ovarian cancer had the lowest chances of recurrence if CRS-HIPEC was used together with conventional treatment plans.

Morbidity Rates

- CRS-HIPEC was related to postoperative morbidity, which was indicative of the technical demand andİNPUT invasive nature of the procedure.
- Morbidity rates were between 20% and 50% in these patient populations, with a growing risk seen in frequency of comorbidity and age.
- Comorbidities observed were infection such as wound, septicemia, anastomosis leakage, haematology toxicity, anaemia, leukopenia and gastrointestinal such as ileus bowel perforation.
- The focus of the studies was on the leadership of perioperative management and surgical measures to reduce the risks of morbidity.

Mortality Rates

- The overall mortality rates were generally less than or equal to 5% throughout most studied cases.
- Independent predictors of worse survival included high age, high PCI scores, worst performance status, and suboptimal debulking.
- It was pointed out that strict compliance with the principles of enhanced recovery and proper patient selection led to a decrease in perioperative mortality.

Prognostic Factors:

- Factors impacting prospectively observed clinical outcomes included PCI, CC scores, histological type of cancer and the baseline Karnofsky performance status.
- All the patients with PCI of 10 and CC-0 or CC-1 had better OS and PFS.
- Patients who were younger and had favourable performance status (e.g., ECOG of 0 or 1) had less morbidity and higher mortality rates.
- Worse survival was recorded among patients with high PCI values, incomplete cytoreduction, or signs of tumour aggressiveness (for example, poorly differentiated adenocarcinoma).

Comparison Across Cancer Types:

- The highest increase was in colorectal and ovarian cancers; the morbidity rates in these patients were lower than in gastric cancer patients.
- Appendiceal cancer had the best prognosis, although some investigations indicated a five-year survival of over 80 %.
- The results with gastric cancer were slightly less favourable due to the inherent aggressiveness of the disease and the difficulties in getting optimal cytoreduction.

Quality of Life (QoL):

- Some of the referenced work pointed to the general aspects of the quality of life (QoL) of patients with CRS-HIPEC concerning symptoms and functional status.
- The level of QoL improvement was significantly higher in long-term survivors; the QoL mostly deteriorated due to surgery-related morbidity, but only temporarily.

Safety Considerations:

- The range of survival benefits and measured procedural risks emphasise the selective approach to patient management and the work of highly specialised interdisciplinary teams.
- The need to increase the use of protective measures

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DOI:10.26502/jsr.10020414

in perioperative care and to implement change for compliance with standardised medical protocols was singled out as central to better clinic results and reduced health risks.

Quality of Life

Evaluating the benefits of CRS + HIPEC for patients with PC consists of an important aspect – the effect of this surgery on the QoL of the patient. It is widely recognised that CRS-HIPEC can enhance the physical survivorship of these patients. However, patients' overall quality of life is a crucial concern since the procedures often entail significant invasiveness and patients are usually diagnosed at an advanced stage of the disease.

Many of the papers have noted that, although relatively few patients significantly improve QoL following CRS-HIPEC, those patients who experience this benefit are often those with long-term survival. Before receiving any therapy, patients with PC have marked symptoms, which consist of abdominal pain, ascites, GI obstruction, etc., which have a significant and negative impact on quality of life. CRS-HIPEC manages the above symptoms because the treatment expunges tumour mass and handles the microscopic disease that brings about such symptoms, improving a patient's functional status. For instance, patients also complain of pain and painful feelings from ascites, and after unwanted treatment, they complain of less pain and, therefore, improved physical health and movement.

However, there is more to explore about the quality of life since CRS-HIPEC is not without its side effects, especially within the first weeks after surgery. A significant morbidity accompanies it, and the resulting postoperative convalescence may be physically and mentally demanding. Several complications of the interventions, notably infective, gastrointestinal and hematologic toxicity, can significantly reduce QoL temporarily, making patients bedridden and more reliant on medical interventions. Furthermore, the length of the surgery depends upon the severity of the patient's pathology and the extent of the surgery, so it causes fatigue and a temporary loss of physical activity. Feelings can also be disturbed in patients. They develop symptoms of anxiety or depression or even uncertain options about their condition, particularly in case of relapse.

However, numerous investigations indicate that QoL increases with disease stage, especially for patients with favourable cytoreductive outcomes and negligible complication severity. Namely, patients note heightened QoL within six to twelve months after the operation and above the baseline treated levels. These changes are most pronounced regarding physical functioning, reducing pain, and managing emotions. Those included a belief in receiving potentially curative treatment and improving the psychological outcome through enhanced OoL, adding to the QoL.

There are differences in long-term QoL results by stage and primary cancer, the extent of cytoreduction, and comorbidities. In the present study, to our surprise, the patients with colorectal or ovarian cancer seem to have better QoL outcomes as compared with the gastric cancer AP firmness, which may precisely be related to the disease nature, operation difficulty, and postoperative convalescence interval. Furthermore, the long-term survivors indicate a higher QoL, implying they are the axis and can more efficiently undertake day-to-day activities and be more independent.

Thus, emergency social support and rehabilitation services are essential in improving QoL after CRS-HIPEC. Strengthened social support from families, friends, or other caregivers and medical practitioners prepares the patients to deal with the physical and psychological ramifications of the ailment.

Surveillance benefits and QoL remain relevant priorities when selecting patients for CRS-HIPEC. This, however, means that patient selection regarding performance status, tumor load and prognosis should be done critically to enable the procedure's benefits to outweigh the risks involved. Paid decision-making must involve the patient as an informed client regarding the pros and cons of the CRS-HIPEC to achieve the best possible goal-post that aligns with the patient's expectations.

Factors Influencing Outcomes

Tumor Type:

- Several authors have described how the type of primary tumour plays a role in determining the results of CRS-HIPEC.
- Colorectal cancer: The authors declare improved overall survival (OS) and progression-free survival (PFS) rates in metastatic colorectal cancer patients and median OS greater than 40 months in best-selected cases.
- Ovarian cancer: Interval debulking surgery with CRS-HIPEC has demonstrated favourable outcomes when implemented in interval debulking, including PFS and OS, particularly in platinum-sensitive diseases.
- Gastric cancer: Outcomes are less favourable, with median OS usually ranging between 15 and 30 months, which captures the virility of the disease.
- Appendiceal cancer: The longest survivals are reported in appendiceal cancer wherein median OS is frequently over 60 months, although for unfavourable histologies similar to PMP.

Tumor Burden:

- Crs-hip failure may be predicted by tumour volume load or surface area, and the most critical measurement is the degree of tumour burden, usually measured by PCI.

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DOI:10.26502/jsr.10020414

- Low-risk patients (PCI≤10) have a better prognosis than high-risk patients with improved OS and PFS.
- PCI >20 indicates increased surgical risk, morbidity, and diminished surgical mortality benefits.
- Several authors have proposed an upper PCI threshold above which CRS-HIPEC might be non-effective; hence, pre-operative imaging and staging are recommended.

Surgical Completeness:

- Of all the factors, completeness of cytoreduction, as determined by the CC score, is one of the most potent indicators of outcomes.
- There is a significant difference in OS and PFS in patients with CC-0 (no visible residual disease) and CC-1 (the extent of residual disease is >2.5mm).
- The clinical implications we derived from the analysis of this study demonstrate that patients with CC-2 or CC-3 scores, that is, residual disease greater than 2.5 mm, have relatively poor prognosis, highlighting the significance of complete cytoreduction.
- Research shows that the surgeon's technical skill and years of experience were dictate whether a patient's tumour can be removed entirely based on the tumour burden and adhesion (Zanoletti et al., 2019).

Patient Factors:

- **Performance Status:** The patients' performance status at the start, usually assessed by the Eastern Cooperative Oncology Group (ECOG) scale, is inherently critical to the results. The advantages in terms of survival and morbidity are associated with ECOG scores of 0 and 1 in patients.
- **Age:** Elderly patients can receive CRS-HIPEC if they have fewer comorbidities, and overall, younger patients have improved outcomes because the tumour is less likely to have penetrated physiologically sturdy tissues.
- **Nutritional Status:** In particular, low BMI, including in adult patients with cachexia or malnutrition, ensues higher morbidity and lower survival rates, emphasizing the importance of the optimal nutritional status before surgery (Juliana et al., 2024).
- **Comorbidities:** Patients with one or more other diseases (e.g., cardiovascular disease, diabetes) are at increased risk in the perioperative period and have poorer outcomes.
- **Psychological Resilience:** Those who dealt with their psychological health and developed coping skills during their CRS-HIPEC treatment seemed to fare better in their post-treatment lives.

Histological Factors:

- Tumour histology and differentiation remained highly significant in the patient's outcome.
- Other factors, patient prognosis, depend on the tumour grade – well-differentiated or low-grade tumours have a much better prognosis than poorly differentiated or high-grade tumours, e.g., pseudomyxoma peritonei.
- It has been shown that the mucinous subtypes generally have a better prognosis than the serous or signet-ring cell carcinomas.

Chemotherapy Protocols:

- In HIPEC, the selection of the chemotherapeutic agents contributes to the results.
- Oxaliplatin is often a component of adjuvant therapy for colorectal cancer, primarily offering improved PFS while maintaining reasonable tolerance.
- Cisplatin has been the first choice of treatment in ovarian cancer as it has an enhanced survival rate, especially in platinum-sensitive tumours.
- Drugs like Mitomycin C are typically employed in appendix carcinoma, and few colorectal carcinoma have highly effective outcomes in low-grade malignancy cases.
- The period of a given protocol, for example, 30 – 120 min, and the selection of appropriate temperature are also significant concerning cytotoxicity without toxicity.

Institutional Expertise:

- Outcomes significantly depend on the surgical team's specialization level and the institution's interaction with CRS-HIPEC.
- Surgical completeness, morbidity, and survival are higher in high-volume centres staffed by specialized and extensive coordinated multidisciplinary teams than in those low-volume centres.

Perioperative Care:

- ERAS means less morbidity and shorter hospital stays; ERAS represents 'Enhanced Recovery After Surgery.'
- Enhanced ultrafiltration, early mobilization, and using an array of nonopioid pain medications help patients enjoy better outcomes as we advance.

Follow-Up and Monitoring:

- Subsequent examination and close monitoring are essential for the timely identification of recurrence, which is a common feature even after CRS-HIPEC.
- Imaging procedures and biomarkers CEA, CA-125, etc., guide the appropriate time for interventional treatments and secondary therapies (Juliana et al., 2024).

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DOI:10.26502/jsr.10020414

Adverse Events

Inherent to cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), patients undergo surgery with a high risk for adverse events due both to the extent of surgery and the high toxicity of the developed chemotherapy regimen. They can affect early and late surgical periods and require optimal pre-operative, intraoperative, and postoperative care and intervention.

The exact rate of complications after CRS-HIPEC is not well defined, but morbidity is quoted to range from as low as 20% to as high as 50%. Moghimi and colleagues described common side effects in about 70% of the patients who received cytarabine and other agent drug combinations, such as infection, gastrointestinal disorders, hemorrhagic events, and renal dysfunction. Among the infectious complications, SSIs, sepsis, and in-tra abdominal abscesses are the most common; these require antibiotics, drainages or even extended hospital stays. GI-related mortalities remain a substantial threat, including anastomotic leakage, bowel perforation, paralytic ileus or any other issues which may necessitate re-interventions or indeed require supportive care with morbid outcomes. Hoskins and co-workers indicated that these complications are likely in patients with high tumour burden, extensive peritoneal resection or pre-operative malnutrition.

Another side effect is hematologic toxicity, prominent in cases when patients receive myelosuppressive agents such as Cisplatin or mitomycin C in HIPEC (Karimi et al., 2024). Cytopenias, anemia, and leukopenia, in particular, have been identified as a means of prolonging the healing process and increasing the patient's vulnerability to infections. Close and regular monitoring of the blood counts in such patients is critical to managing these toxicities, and the typical supportive care measures include the use of blood products and growth factor support. Compared to other chemotherapy drugs, cisplatin-based HIPEC is especially likely to cause renal toxicity, especially if the patient has become dehydrated or has pre-existing renal compromise. This danger is best managed by frequent hydrations, appropriate use, and measured portions of chemotherapeutic substances.

Despite this, cardiovascular issues may be realised in clients due to the movement of fluids, the effects of a prolonged anaesthesia time and systemic inflammation elicited by CRS HIPEC. This includes arrhythmias, low blood pressure and, in the worst-case scenario, heart failure. These risks should be closely monitored, and intraoperative and perioperative adjustments of hemodynamics should be done closely. Pulmonary modalities like pneumonia or pulmonary embolism are also described in some cases, requiring mobilisation, anticoagulation and respiratory support (Rosovsky et al., 2020).

Complications of CRS-HIPEC are not only seen in physical health, but they have a life-altering effect on the patient psychologically as well. Mood disorders, post-surgical cognitive Impairment and depression are frequent, especially where the prognosis is poor or recovery is expected to be lengthy. These are significant problems, and counselling and other psychological interventions are crucial in tackling these and enhancing the observed quality of life during recovery.

Despite these challenges, the perioperative mortality for CRS-HIPEC has declined over the years mainly as a result of the technical progression of surgery for these diseases and improvement in pre-operative, intraoperative and postoperative care as well as patient selection. Early mortality has been reported to be between 1 and 5 percent on average for high throughput facilities. Predictors of an increased mortality rate are age, PCI, incomplete cytoreduction, and comorbid conditions. Apart from the CRS-HIPEC procedure having significant mortality risks, a thorough pre-operative assessment of these patients is necessary to identify potential postoperative complications and enrol only patients most likely to benefit from this procedure (Xue et al., 2021).

Treatment for complications of CRS-HIPEC involves identifying them early, coupled with the assistance of cross-sectional practitioners and compliance with the enhanced recovery principles. Measures, including prophylactic antibiotics, good fluid balance, and careful surgery, have been found to dramatically reduce the number of incidents of these complications (Pioli et al., 2020). The other therapies that are vital in ensuring the patients recover and do not stay for long in the hospital include early mobilisation feeding support. In high-risk patients, postoperative surveillance in intensive care units facilitates early management of complications (Pioli et al., 2020).

Hence, although CRS-HIPEC is complex and confers a specific risk of complications, any adverse event is navigable with strict perioperative planning and care coordination. The advantages of CRS-HIPEC for enhancing the prognosis and quality of life in patients with peritoneal carcinomatosis are that it can overcome the risks when the procedure is offered to selectively chosen patients at dedicated centres. The proliferation of these protocols, improvement of recovery procedures, and strengthening of patient care services are critical to decrease the incidence and improve the short and long-term quality of life for patients receiving this intricate, yet potentially curative, therapy.

Discussion

Interpretation of Findings

The results observed in the context of the systematic review suggest that CRS and HIPEC can extend the patient's survival and decrease the likelihood of recurrence in the PC case. The findings, though, are dissimilar across the studies because of differences in study method, patients, types of

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DOI:10.26502/jsr.10020414

cancer, operations, and chemotherapy schedules. Most of the investigated OS trends were observed to have improved significantly, especially in patients with colorectal, ovarian, and appendiceal cancers (Harper et al., 2022). The median OS for CRC was 30–60 months for patients who underwent complete cytoreduction (CC-0 / CC-1). Specifically, in ovarian cancer, combined CRS-HIPEC, especially during interval debulking surgery, increased median OS beyond 50 months. Cancer located in the appendix had the best prognosis; many reports found OS was above 60 months for patients with low-grade histology, such as pseudomyxoma peritonei. Outcomes for gastric cancer were somewhat mixed, with median Os ranging between 15-30 months, indicating the aggressiveness of the disease as well as the inherent difficulty of achieving effective debulking (Mahvi et al., 2018).

Yet again, there was a significant enhancement to the patients' progression-free survival (PFS). In colorectal cancer, PFS varied between 12 to 24 months based on tumour load, completeness of cytoreductive surgery, and type of chemotherapy regimen. In ovarian cancer, published works describe MF at progression with PFS of more than 20 months, notably in the platinum-sensitive population. A similar trend was recorded for PFS in gastric cancer, although there was reported heterogeneity about tumour characteristics and patient population. Cancer of the appendix once more proved to have the best results, and better PFS was noted in patients with low-grade malignancies. These results suggest that CRS-HIPEC's ability to slow disease progression depends on tumour type, histology, and completeness of cytoreduction (Elashwah et al., 2022).

Recurrent rates were significantly lower for CRS-HIPEC patients than for patients who underwent systemic chemotherapy only (Morano et al., 2018). Every analysed work revealed that the application of CRS-HIPEC was associated with a reduced rate of cancer reoccurrence in the case of colorectal and ovarian carcinomas if used in patients with low PCI and high rates of optimal debulking. The recurrence rate was found to be higher in gastric cancer studies, which confirms the fact that the disease progresses rapidly and its therapeutic interventions are limited. Low-grade appendiceal cancer showed the lowest recurrence rates among all the malignancies; thus, the analysis supported the use of CRS-HIPEC in managing the progression of this lesion (Nikiforchin et al., 2023). In all cancer types, recurrence was a highly significant predictor of residual disease (CC-2 or CC-3), underpinning the need for cytoreduction during tumour resection.

Morbidity was also observed across the studies, with the overall reported percentage varying between twenty and fifty per cent. Some of the surgical complications reported were infection, anastomotic breakdown, hematologic toxicity, and gastrointestinal dysfunction. They have included the differences in surgical skills, the experience of the institutions involved, and the degree of complication control protocols practiced during surgeries. Increased PCI and large extent of resection were correlated to increased morbidity, while compliance with ERAS protocols ameliorated morbidity and enhanced postoperative recuperation. Mortality was relatively low, standardised to value between 1-5% of most research, thanks to improved surgical procedures and care pre- and post-operation. The factor that allowed for reducing complication rate was directly connected to the institutional volume and expertise of the surgical team, which underlined the necessity of the CRS-HIPEC procedure in high–volume centres (Sedighim et al., 2023).

Patient selection was identified as the key indicator of the outcomes. For OS, PCI $\leq$ 10 was significantly better for OSI and PFS, and the patients had less morbidity than the group with PCI > 20. Tumour histology and differentiation were also major success indicators in this treatment area, with low-grade tumours like pseudomyxoma peritonei giving the best results in this treatment area (Govaerts et al., 2021). Another predictor was the baseline patient performance status using the ECOG, which showed that patients with ECOG scores of 0 or 1 had better post-treatment outcomes. Other factors that impacted recovery and prognosis included age and nutrition preoperatively, again highlighting the need for optimisation.

Consequently, the type of chemotherapy drug or HIPEC regimen correlated to prognosis in this meta-analysis. Oxaliplatin was mainly applied in colorectal cancer, and the research showed moderate effectiveness and reasonable side effects. Cisplatin remained the agent of choice in ovarian cancer and showed an increased survival advantage in patients with platinum-sensitive disease. Mitomycin improved the results in some appendiceal and parts of some colonial rectal cancers, especially in low-grade malignancies (Yurttas et al., 2018). The HIPEC duration used in the different studies ranged from 30 to 120 minutes, while the temperature most often standardised according to HIPEC guidelines was also different for other studies. These variations mean that more standardisation of HIPEC protocols is needed to help improve the results (Yurttas et al., 2018).

When the evaluation was based on tumour types, CRC and ovarian cancers showed the most significant survival gains when treated with CRS-HIPEC. Appendiceal cancer fared overall the best, which is logical given that this disease is usually more indolent and quite amenable to cytoreductive surgery if necessary (Ryall, 2021). Oesophageal cancer survival rates were better, while gastric cancer survival rates were comparatively poor due to a higher aggressive index and sub-optimality of cytoreductive procedures. These points demonstrate a need for approach adjustments of CRS-HIPEC regarding the kind of tumour and assessment of the disease and the patient.

Citation: Ahmed Ayman Yakout, Omar Kusay Hamrawi, Awad Saeed, Sara Basel Younes, Thrisan Sudharsan, Abhishek Rajesh Panikar, Ibraheem Mohammed Saeed Aldujaili, Mohamd Mahmoud Said Ghaly, Lina Ahmad Omar Alhaj, Hamza Abdelbagi Elfaki. Outcomes of Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis. Journal of Surgery and Research. 8 (2025): 20-37.

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DOI:10.26502/jsr.10020414

Therefore, CRS-HIPEC exhibits promising trends in the increase of survival and lowering of recurrence rates in patients with peritoneal carcinomatosis. However, the results depend on the tumour type, volume, extent, surgical path, and individual characteristics. The outcomes proposed in this article suggest that prospective individuals' selection, organisational experience and interdisciplinary cooperation could produce the beneficial effect of CRS-HIPEC with minimal adverse impacts. More work must be done to adjudicate procedure specifics, better define patient populations, and better unify research metrics for success to make results more meaningful and comparable (Moffatt et al., 2022).

Current treatment with CRS-HIPEC is for patients with peritoneal carcinomatosis. A significant shift indicates a new way of thinking about the result and the possibility of more prolonged survival and better control over the disease. However, the review makes it clear that the outcomes are complex and depend on various factors, and, therefore, the interpretation of the results cannot be exhausted within the frames of simplistic conclusions (Jeffries et al., 2021). Each of the studies reveals that tumour biology and patient features, in combination with treatment regimens, are crucial for evaluating the efficacy of the CRS-HIPEC

Among them, the tumour biology, including histological type, grade, and origin of the primary tumour, has been considered to have the most significant impact on the results. Local disease like pseudomyxoma peritonei originating from appendiceal cancer belongs to the lowest grade and best prognosis tumour type, which significantly benefits from the agent of CRS-HIPEC. As for the histopathological grade, high-grade and poorly differentiated tumours are more challenging to manage, and the survival benefits are not as remarkable as those in early-stage gastric cancer. These results support the utility of such models to determine tumour-specific reactions to CRS-HIPEC and to identify patients with high probabilities of benefit from this procedure (Green et al., 2023).

One more sign derived from the studies is surgical CU completeness. Again, the rates of CC-0 or CC-1 were revealed to be correlated with better survival and recurrence characteristics. It is critical to strive to attain the best result with cytoreduction, which is why such surgery requires proficiency and experience (Friedberg et al., 2019). Some studies found that centres with high volume in CRS/HIPEC perform the procedure with fewer complications and consequently better survival rates, thus the need for its performance in specialised centres with a team of professionals.

Site-specific factors, such as patients' age, performance status, and nutritional status, add to the above-listed factors that may affect outcomes. Patients who were young and had better performance status and fewer comorbidities were more likely to recover and have better outcomes. Enhanced recovery programs, nutritional support, and intra-operative or pre-and postoperative care minimised patients' mortalities (Nilsson et al., 2020).

However, side effects are still a problem regarding this treatment. Infections, gastrointestinal difficulties, and haematologic toxicity highlight the importance of close follow-up and supportive care within the postoperative period. The outcomes provide the rationale for the message that speaking in a balance or choosing between survival benefits and risks shows the most outstanding results.

Strengths and Limitations of Evidence

The body of evidence underpinning this systematic review is informative about cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal carcinomatosis (PC) (Jacobson et al., 2019). Numerous features contributing to research validity and reliability are outlined below, but the weaknesses in generalising the findings are also discussed first.

The heterogeneity of study designs is also a considerable advantage of the examined proof. RCTs, cohort studies, and retrospective analyses allow for accurately assessing the CRS-HIPEC results. RCTs, especially, guarantee high internal validity since they use stringent methodology and randomisation as well as the control group. These trials adequately control for variables in a way that allows the effects of CRS-HIPEC on survival and recurrence to be determined with a relatively high degree of accuracy. This comprises prospective cohort studies that present actual clinical cases in a certain population, giving a picture of the real-world patient population. Because retrospective studies are likely to be introduced to bias, they supply long-term results and infrequent adverse events that might be missed in trials of shorter periods (Caparrotta et al., 2019).

The comprehensive documentation of endpoints such as the OS, PFS, and recurrence rate is the advantage of the systematic studies. These metrics are proposed and calculated unequivocally; thus, the results can be compared to produce the desired synthesis. Furthermore, PCI and CC scores, as well as many other indices, are employed in numerous investigations, lending objective character to the reflection of tumour load and the efficacy of the surgery. This characteristic makes subgroup analysis easier and generalizing the results across cancer types more feasible.

Selection criteria for patients are another strength that must be considered when assessing the process of CRS-HIPEC. Patients and methods sections of many studies contain descriptions of PCI, histology, PS, and comorbidities under inclusion criteria. These parameters are crucial for selecting proper candidates to introduce into the CRS-HIPEC program, in which the potential benefits are deemed to exceed

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DOI:10.26502/jsr.10020414

the risks. The presence of the study and the identification of prognostic indicators improve the validity of the work based on the variables that affect survival, including the tumour type, residual surgery, and chemotherapy protocols...

Nonetheless, several constraints deserve to be mentioned. One is the variation of patients, tumours, and treatment modalities in the included trials. Although such diversity emulates the actual practice, heterogeneity is additive to complications that hinder straightforward comparison and reduce generalisability. For example, the selection of the chemotherapeutic agents and HIPEC regimens continue to differ regarding duration, temperature, and concentration. Such discrepancies hamper efforts to define superior regimens and bring about treatment regimen uniformity.

Another drawback is that many of the present studies can be reviewed retrospectively. As a post-hoc approach, retrospective designs are always associated with issues like selection bias, incomplete observational data, and regard to confounding factors. Although these studies offer valuable long-term data, one has to bear in mind some limitations of the findings: the data were obtained with a non-random sample; therefore, systematic errors, however minor, are possible. Of course, prospective cohort studies, even though theoretically superior to the previous type, are by no means devoid of bias, especially in non-randomized settings where patients' allocation may predetermine the outcome.

In some of the included studies, the sample sizes would appear small; this poses a problem in evaluating results of interest for significant differences or detecting low-frequency complications. Most research directs attention to one or some kinds of cancer or some patients with such conditions, meaning that there is low external validity. Further, some follow-up time in the studies reported is inadequate to determine long-term results, including recurrence rate and delayed complications. This may be of most significance in cancers such as appendiceal and ovarian cancer, wherein there may often be long-term survivors who are at increased risk for developing CVD.

Another methodological concern is the use of complications and adverse events and how they are presented. Most earlier publications report morbidity and mortality; definitions, severity grading, and documentation of complications are not precise. This confusion makes it challenging to meta-analyze studies related to the safety of CRS-HIPEC and compare the complication rate of the procedure. In addition, definitions of quality of life are often well-rounded, reflecting a significant arbiter for assessing the general worth of CRS/HIPEC, given the post-surgery complications.

The second issue is publication bias. The significant survival gains and low complication rate of positive results may be published, while negative or neutral results may remain unpublished. This prejudice influences the available materials and can overstate the effectiveness of CRS-HIPEC. A lack of negative results published in the literature makes balancing the risks and benefits difficult.

Finally, the role of institutional and surgeon experience remains; again, this variable is often unmeasured and/ or undertreated in much of the evidence base. Centres with high operations volume and dedicated teams have a better prognosis. Still, the absence of standard measures of institutional experience prevents the formulation of general conclusions regarding the impact of specialization. For these reasons, the results should be viewed within institutional capacity and surgical expertise.

Lastly, there is a shortage of robust studies comparing CRS-HIPEC with other treatment methods, including systemic chemotherapy alone or other regional approaches. ALTOGETHER, existing data demonstrate the activity of CRS-HIPEC; however, the lack of direct comparisons between CRS-HIPEC and other treatments precludes definitive identification of the circumstances in which the former is preferable to the latter. Further research should focus on making direct comparisons to clarify the differences in the benefits and threats.

It can be stated that compared to other neoplastic diseases, the evidence base for CRS-HIPEC is substantially strong regarding methodological characteristics presented by the studies, including the variability of design, the uniformity of outcome measures, and the consideration of prognostic factors. These strengths form the basis for designing the evaluation and effectiveness of peritoneal carcinomatosis using CRS-HIPEC. However, some limitations must be considered while concluding the present investigation: The studies included in the analysis are heterogeneous, including prospective and retrospective study designs and varied sample sizes. They suggest that the reduction of these limitations through adherence to a standard protocol, the use of a greater number of centres/ institutions, and the use of better-defined quality-of-life measures were enrich the body of evidence and clarify how CRS-HIPEC should be best employed (Xia et al., 2023).

Implications for Clinical Practice

These implications suggest that the experiences highlighted in this systematic review should interest clinicians and pathologists in identifying clinical practice patterns for patients with PC and considering CRS with HIPEC for a broad spectrum of cancers. Agreeing with the findings of other studies, this review consolidates the available evidence on overall and disease-free survival, recurrence rates, safety profile, prognostic markers, and practical recommendations for patient selection, multimodal therapy, and care during and after surgery.

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DOI:10.26502/jsr.10020414

This is why one of the most direct clinical implications of the study highlighted here is the necessity for patient selection. PelvEx Collaborative (2022) stressed that CRS-HIPEC is a time-consuming and expensive invasive technique; therefore, sparing those most likely to benefit from the procedure is crucial. The data indicate that obtaining better OS and PFS can be associated with PCI, ECOG, and comorbidity scores. For these patients, chemotherapy with CRS-HIPEC has a curative or life-extending ability that cannot be achieved with systemic chemotherapy alone. In contrast, the low likelihood of benefit and increased risks of morbidity and mortality exist in patients with high PCCI scores, poor performance status, and extensive extra-peritoneal metastases. Including PCI and performance status in the treatment planning allows for better identification of suitable candidates for CRS-HIPEC (Acs et al., 2024), thus utilizing it to maximum benefit and avoiding complications for patients who do not need this procedure.

The second potential consequence is that the CRS-HIPEC needs to be adjusted depending on the type of tumours. The review also points out the heterogeneity of the findings based on cancer type, with colorectal, ovarian, and appendiceal cancers being the most responsive to Ramucirumab. Patients with colon or rectal cancer with isolated peritoneal metastases and no other systemic disease also gain substantial survival benefits when undergoing CRS-HIPEC in addition to systemic chemotherapy. In ovarian cancer, CRS-HIPEC has been applied to improve both PFS and OS, mainly when used during interval debulking surgery in platinum-sensitive disease.

Low-grade appendiceal malignancies such as pseudomyxoma peritonei have excellent results, confirming that if patients are selected appropriately, CRS-HIPEC is the gold standard of care for such patients. Nevertheless, for gastric cancer, there is not enough evidence for the routine use of this therapy (Smyth et al., 2020), and the authors called for careful selection of patient candidates for this strategy and future studies of this advanced malignancy to establish the benefits of this therapy.

Future Directions

Despite the strong evidence for CRS-HIPEC, several research limitations remain, and specialized future research is warranted to optimize CRS-HIPEC for improved outcomes. This allowed for more effective evidence-based recommendations and answers to these gaps in patient care.

Their crucial flaws include the fact that, for the most part, there are no established guidelines for CRS-HIPEC. The discrepancy in chemotherapeutic agents, dosages, HIPEC sessions, and temperature variations makes it difficult to compare results and identify an ideal protocol. Further studies are needed for multi-centered RCTs comparing the efficacy of different HIPEC regimens according to the primary tumour type. Such trials should be designed to set the best regimes for the use of drugs and procedural schemas that were followed across healthcare practices and thus increase patients' efficacy.

Another opportunity is the evaluation of CRS-HIPEC for tumour types that have not been investigated in detail, such as mesothelioma or gastric cancer. As for the efficacy of CRS-HIPEC in other cancers, few investigations have been reported, although CRS-HIPEC was initially used in many cancers. To increase the number of patients that may benefit from CRS-HIPEC or to help customise treatments for patients undergoing CRS-HIPEC, more could be learned about what makes a tumour specifically responsive to CRS-HIPEC at a molecular and genetic level.

Patient selection criteria also must be further defined. It might be comprehensible that traditional prognostic scores such as Peritoneal Cancer Index (PCI) or Completeness of Cytoreduction (CC) cannot comprehensively assess patient and tumoral characteristics that might affect the outcomes. The following future studies of the case should involve the utilization of primary imaging modalities, chemical and marker, and machine learning models to boost the pre-operative assessment and improve the chances of a successful result. Such advancements may enhance the possibility of differentiating patients more effectively and minimize various challenges associated with faulty treatment.

Other proposed future research includes assessing the effect of CRS-HIPEC on QoL in the long run. Although various reports highlight early onset postoperative complications and survival advantages, few focus on how such factors affect QoL. Future trials using an objective method of quantifying QoL with physical, emotional, and social components should be considered to determine whether or not the benefits of CRS-HIPEC outweigh the corresponding difficulties.

Lastly, cost-effectiveness analyses should not be left behind in future studies. HIPEC is a more invasive hybrid treatment, and the present study aimed to determine whether its cost in terms of survival and QoL benefits is relevant to becoming a standard of care as part of healthcare policies. Other specific areas that might offer to hide valid data comparing CRS-HIPEC to other emerging theoretical therapies include:

Conclusion

This SR synthesizes the literature on CRS + HIPEC for treating PC according to key parameters such as efficacy, safety, and clinical relevance. These findings also highlighted the opportunity for CRS-HIPEC as a game-changing

Citation: Ahmed Ayman Yakout, Omar Kusay Hamrawi, Awad Saeed, Sara Basel Younes, Thrisan Sudharsan, Abhishek Rajesh Panikar, Ibraheem Mohammed Saeed Aldujaili, Mohamd Mahmoud Said Ghaly, Lina Ahmad Omar Alhaj, Hamza Abdelbagi Elfaki. Outcomes of Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis. Journal of Surgery and Research. 8 (2025): 20-37.

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DOI:10.26502/jsr.10020414

approach to specific patients- demonstrating both increases in survival and decreases in recurrence compared to other treatments for certain cancers, including colorectal, ovarian, and appendiceal cancers. Nevertheless, these advantages must be balanced against the technical intricacy of the procedure, its substantial mortality, and requirements to correct patient choice and multiple teamwork.

It also remains noteworthy that all the studies have shown an overall survival and progressive-free survival benefit to patients receiving CRS-HIPEC. While the median OS of colorectal cancer is more than 40 months, similar effects in ovarian and appendix cancer are even detected in O-CR=1,2, even better if the optimal cytoreduction was achieved CC-0 or CC-1. Pseudomyxoma peritonei and other low-grade histologies have the best prognosis in appendiceal cancer, with a median OS above 60 months in many cases. On the other hand, the prognosis for gastric cancer is still less satisfactory owing to the invasive character of the tumour and the limited potential of radical surgery.

The review also emphasizes tumour biology, load, and surgical resectability as other factors influencing the outcome. PCI is a crucial factor in evaluating tumour spread. Low PCI is associated with better OS and PFS and less recurrence. Like the declaration that optimal cytoreduction is possible only if performed by experienced surgical oncologists, the degree of cytoreduction determines survival benefits cannot be overemphasized. Consistency regarding tumour type, histology, and surgical resection confirms that the process has to be customised according to the profile of the diseases in each patient.

Nevertheless, the CRS-HIPEC is accompanied by high levels of morbidity, with complication rates varying between 20 and 50%. Most patients' side effects are infections, gastrointestinal disturbances, and haematologic complications. Even though mortality during hospitalisation is low (1 to 5 percent in large-volume institutions), complications are best addressed by thoughtful pre-operative, intraoperative and postoperative care and adherence to ERAS standards. These results underscore the paramount importance of the multidisciplinary approach to de-risking and enhancing clinical outcomes, in which surgical oncologists, medical oncologists, anesthesiologists and specialists in supportive care are involved.

Another important factor is quality of life (QoL). Short-term symptoms of reduced physical performance during the early periods after surgery are common. Still, improvements are usually seen in the long term concerning eradicating symptoms, physical functioning, and psychological well-being. Notably, the survival benefits and QoL trade-off indicate that allowing patients to participate in the decision-directing efforts at what matters most to them contributes to effective treatment decisions.

From a clinical point of view, CRS-HIPEC is a leap forward in PC management, most notably for the previously considered poor prognosis of cancer. However, the conclusions in this review stress that patient selection should be made more selectively according to PCI results, performance status, and molecular characteristics of the tumours in patients undergoing cytotoxic therapy. Not all patients derive equal and optimum benefits from CRS-HIPEC, besides being highly dependent on a patient's proper identification and treatment for the best method to apply. Also necessary is the requirement for focalising CRS-HIPEC procedures in specialised centres with large practice volumes and highly qualified interdisciplinary teams.

Several gaps in the literature should be filled to enhance the utility of CRS-HIPEC in clinical practice. For HIPEC, standardisation concerning chemotherapeutic agents used, the dose, and analysable procedural parameters were eliminate variability. Extensive prospective investigations for evaluating the QOL and cost outcome must be performed to give a comprehensive account of the effects of the procedure. Therefore, the further development of CRS-HIPEC should consider extending this treatment to other types of tumour, including new biomarkers and imaging modalities for better patient identification.

Therefore, CRS-HIPEC should be considered a highly effective therapeutic modality for treating peritoneal carcinomatosis and can produce survival benefits and disease palliation in patients selected for this procedure. Despite foreseeable obstacles in fine-tuning protocols, dealing with the complications, and addressing the issue of access, the available evidence allows for considering CRS-HIPEC as the cornerstone of PC care. Future research and interdisciplinary work were only strengthen its safety and effectiveness, and its broader usefulness were improve clinical results for individuals with this complex disease (Austin et al., 2018).

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Citation: Ahmed Ayman Yakout, Omar Kusay Hamrawi, Awad Saeed, Sara Basel Younes, Thrisan Sudharsan, Abhishek Rajesh Panikar, Ibraheem Mohammed Saeed Aldujaili, Mohamd Mahmoud Said Ghaly, Lina Ahmad Omar Alhaj, Hamza Abdelbagi Elfaki. Outcomes of Cytoreductive Surgery Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis. Journal of Surgery and Research. 8 (2025): 20-37.

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