

COMPARATIVE STUDY BETWEEN CYTOREDUCTIVE SURGERY ALONE VERSUS CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRA-PERITONEAL CHEMOTHERAPY IN IRAQI PATIENT WITH DIFFUSE INTRAPERITONEAL CARCINOMATOSIS

¹*Mohammed Saad Yas, ¹Aqeel Shakir Mahmood, ²Abbas Ali Hasan

¹Consultant Oncologic Surgeon, FRCS – London.

²M.B.Ch.B, F.I.C.M.S.

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*Corresponding Author: Mohammed Saad Yas

Consultant Oncologic Surgeon, FRCS – London.

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ABSTRACT

Background: Peritoneal Carcinomatosis (PC) remains a major therapeutic challenge. Cytoreductive surgery (CRS) combined with Hyperthermic Intraperitoneal chemotherapy (HIPEC) is increasingly adopted, but local evidence from low- and middle-income settings is limited. We evaluated outcomes of CRS alone versus CRS+HIPEC in an Iraqi cohort. **Methods:** We performed a prospective cohort study of 100 consecutive PC patients (2021–2025) treated with CRS alone (n=50) from total (217 cases) or CRS+HIPEC (n=50) from total (71 cases). Baseline variables included age, sex, primary tumor type, Peritoneal Cancer Index (PCI), and neoadjuvant therapy. Primary endpoints were overall survival (OS) and peritoneal relapse-free survival (PRFS). Secondary endpoint was postoperative performance status. Group comparisons used Welch's t-test when variances were unequal and Student's t-test otherwise; categorical variables were compared with chi-square tests. **Results:** Groups were balanced at baseline: mean age 58.86±7.48 (CRS) vs. 58.46±8.13 years (CRS+HIPEC); PCI 11.00±3.12 vs 10.88±3.44 (both p>0.05). Females comprised 86% in each arm; primaries were ovarian (68%), colonic (12%), gastric (12%), and appendiceal (8%); neoadjuvant therapy was used in 74% per group. CRS+HIPEC achieved longer OS (37.90±16.03 vs 19.42±8.45 months; mean difference 18.48 months; 95% CI 3.38–13.58; p=0.001, Welch's) and longer PRFS (28.34±13.32 vs 15.36±5.58 months; mean difference 12.98 months; 95% CI 8.90–17.06; p<0.001, Welch's). Performance status was better (lower score) after CRS+HIPEC (8.58±2.60 vs 11.06±2.94; mean difference 2.48; 95% CI 1.38–3.58; p<0.001). **Conclusion:** In this single-center Iraqi cohort, adding HIPEC to complete Cytoreductive surgery was associated with clinically meaningful improvements in survival and postoperative function compared with CRS alone, with balanced baseline characteristics. These findings support adopting CRS+HIPEC for carefully selected patients within standardized pathways; prospective multicenter evaluation with time-to-event methods and comprehensive toxicity reporting is warranted.

KEYWORDS: Peritoneal Carcinomatosis; Cytoreductive surgery; Hyperthermic Intraperitoneal chemotherapy; HIPEC; overall survival; relapse-free survival; Peritoneal Cancer Index; Iraq.

INTRODUCTION

Peritoneal Carcinomatosis (PC), defined as the intraperitoneal dissemination of malignant diseases, continues to be the most tragic manifestations of late-stage intra-abdominal cancers, often characterizing patients with primary malignancies of the gastrointestinal

tract (colorectal, gastric, appendiceal carcinomas) and gynecological malignancies (i.e. ovarian cancer).

Traditionally, PC has been characterized as terminal disease status in the past due to the poor outcomes and available therapies associated with PC.

The prevalent approach to managing PC was often palliative in nature - primarily focusing on symptomatic management of malignant ascites, intestinal obstruction, and pain - rather than a long-term disease control strategy.

While systemic therapies using conventional chemotherapy were still standard of care, these approaches often do not penetrate the peritoneal-plasma barrier extremely well and do not provide favorable local tumor response with overall median survival often to 6-24 months, based on the primary tumor type and tumor burden.^{[1][2]}

However, over the last 20 years there has been a major change in the management of PC, introduced as a combined modality approach: Cytoreductive surgery (CRS) followed by Hyperthermic Intraperitoneal chemotherapy (HIPEC).

CRS is defined as the extensive elimination of all visible tumor nodules within the abdominal cavity and may entail several peritonectomy procedures and multi-visceral resections.

Thereafter HIPEC is delivered immediately after CRS via the perfusion of heated chemotherapeutic agents into the peritoneal cavity.

This process intends to eliminate any residual microscopic disease that could not be surgically removed.

The hyperthermia (usually 41–43°C) not only contributes a cytotoxic effect, but also enhances the cytotoxicity of the chemotherapy by increasing drug penetration, impairing tumor cell DNA repair pathways, and alters cancer cell susceptibility to apoptosis.^{[3][4]}

The peritoneal-plasma barrier limits the effective concentration of intravenous chemotherapeutic agents that reach the peritoneal surfaces, which are the main sites of disease in PC.

The HIPEC (Hyperthermic Intraperitoneal Chemotherapy) evaluation delivers chemotherapy directly to the affected area in Hyperthermic conditions, thus maximizing local efficacy while minimizing systemic toxicity.^[5]

Patient selection is vital in identifying who may benefit most from this combined treatment. The Peritoneal Cancer Index (PCI) showed in figure 1, was developed by Sugarbaker as a scoring system to measure the extent and variety of peritoneal disease across 13 regions of the abdomen.

The PCI is a quantitative score that ranges from 0 to 39, the higher the score, the worse the disease. Multiple studies have been conducted demonstrating that patients

with lower PCI scores, typically under 20, are more likely to achieve complete cytoreduction (CC-0/CC-1) and have improved long-term survival outcomes.^[6] Thus, the PCI was developed as an operational tool for surgical planning and prognostic assessment of candidates for CRS and HIPEC.

The study aims to compare the clinical importance of preoperative PCI on clinical outcomes to improve patient selection and assist in clinical decision-making in this patient cohort this study is also compare and evaluate overall, disease free survival, recurrence rates, perioperative morbidity, mortality, and postoperative quality of life outcomes between CRS + HIPEC, and CRS alone, in Iraqi patients with peritoneal carcinomatosis.

METHODOLOGY AND MATERIALS

Study place and time

*Baghdad Teaching Hospital Medical city(CRS),
*and Arabi Private Hospital(HIPEC+CRS).

The data was collected from the 2021 to the 2025 (48 month)

Study design

An analytic cohort design has been chosen for this study.

Selection of the research population

Among 288 cases, (71 CRS with HIPEC)(217 CRS alone) 100 patients were selected, while 188 patients were excluded due to reasons mentioned in the exclusion criteria.

Participants consent

Verbal consent has been obtained from all participants before data collection.

Inclusion criteria

- Adult patients (age ≥ 18 years) with peritoneal carcinomatosis (PC) secondary to gastrointestinal or gynecological malignancies.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 .
- No evidence of extra-abdominal metastases.
- Peritoneal Cancer Index (PCI) ≤ 20 , have shown improved outcomes in patients with lower PCI scores undergoing CRS+HIPEC.

Exclusion criteria

- Unresectable disease.
- Extra-abdominal metastases. (Pulmonary, brain etc.)
- Advanced liver met.
- Poor performance status.
- Contraindications to surgery or Hyperthermic chemotherapy.

Preoperative Evaluation

All patients underwent thorough preoperative assessments, including

* Contrast-enhanced CT scans

*MRI

* Diagnostic laparoscopy if needed.

The PCI was scored preoperatively(dx laparoscopy) based on Sugarbaker's classification, dividing the abdomen into 13 regions and grading tumor implants from 0 to 3, with a maximum score of 39.^[6]

Surgical Procedures

CRS was performed by an experienced surgical oncology team (same team) following the principles established by Sugarbaker, aiming for complete cytoreduction (CC-0 or

CC-1). Procedures often included peritonectomy, bowel resection, omentectomy, and removal of involved viscera.

In the CRS+HIPEC group, Hyperthermic chemotherapy was administered intraoperatively following tumor resection. The closed-abdomen technique was employed, with perfusion of heated chemotherapeutic agents—commonly cisplatin or oxaliplatin—for 60- 90 minutes at 41–43°C.



Figure 1: AT Arabi private hospital A: HIPEC perfusion machine (Performer 3) displaying temperature and circulation data. B: Patient draped on operating table with HIPEC tubing connected. C: Abdomen post-CRS with drains and stoma, dressed for HIPEC. D: OR setup during CRS+HIPEC showing surgical field and equipment.

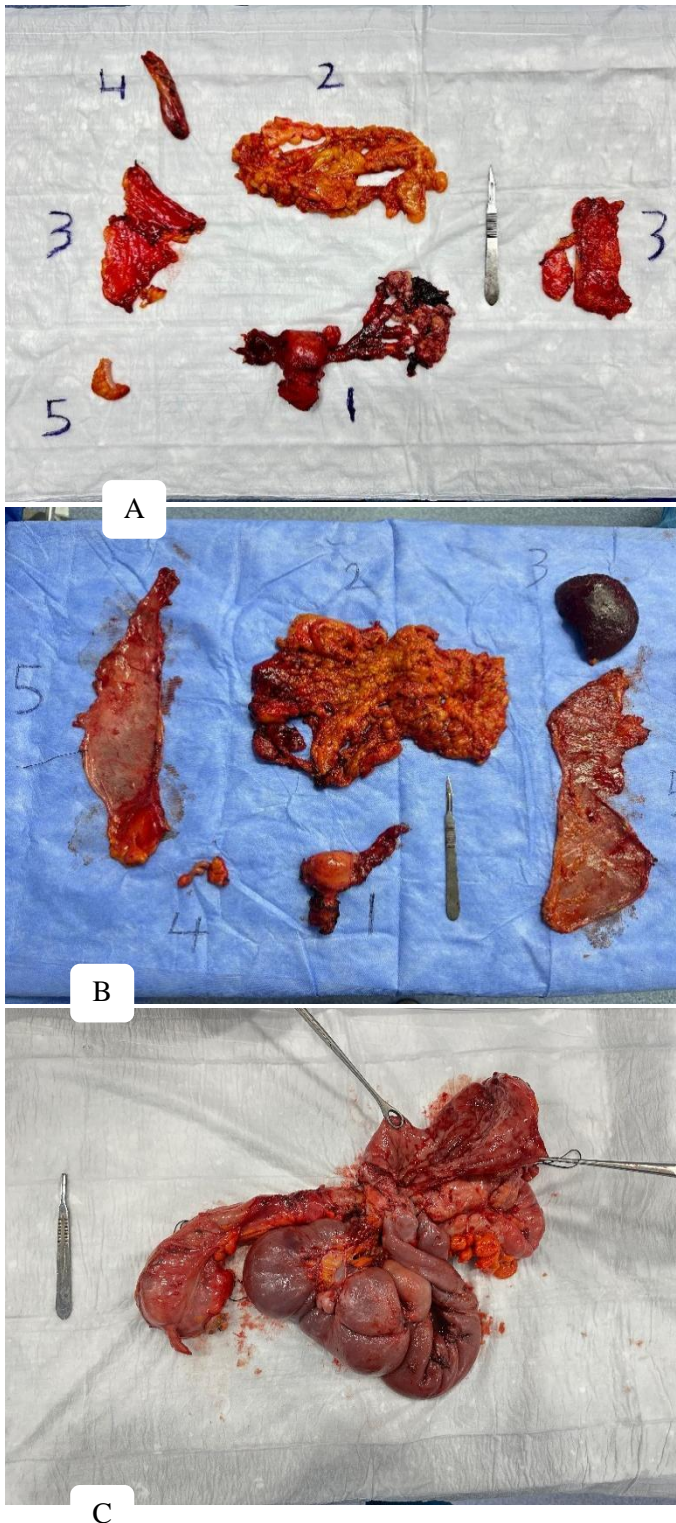


Figure 2: Operative specimens obtained during Cytoreductive surgery and Hyperthermic Intraperitoneal chemotherapy (CRS+HIPEC).

Specimens on white drape (Image A) – Figure 4.
70 years old female with hx of locally advanced left ovarian ca taken neoadjuvant chemotherapy

PCI calculated .fit for CRS with Hipec

Resected specimens from CRS+HIPEC including:
 (1) Uterus with bilateral adnexa.
 (2) Omentum.
 (3) Peritoneal strips.
 (4) Gallbladder. (Multiple stone)
 (5) Appendix.

Specimens on blue drape (Image B) – Figure 4.

77 years old female with hx of right salpingoophorectomy presented with local recurrence high grad met. Serous carcinoma with splenic involvement taken neoadjuvant chemotherapy

PCI calculated by dx lap. Fit for CRS with Hipec

Additional CRS+HIPEC specimens:
 (1) Uterus with bilateral adnexa.
 (2) Omentum.
 (3) Splenic
 (4) Appendix.
 (5) Parietal peritoneum strips.

En bloc bowel resection specimen (Image C) – Figure 4.

49 years old female with hx of CA stomach

Distal gastrectomy done at 2024

Locally advanced recurrence invading tail of pancreas and spleen and part of jejunum

CRS with Hipec

En bloc resection specimen showing small bowel loops with mesenteric tumor deposits and associated peritoneal surfaces removed during CRS.

Data Collection and Variables

Demographic and clinical data were collected, including:

- Name
- Age
- Sex
- Comorbidities
- Type and site of primary tumor
- Time of diagnosis
- Neoadjuvant therapy status
- Interval until tumor relapse
- Peritoneal Cancer Index (PCI) score
- Time of postoperative hospital stay
- Pain scale
- Number of hospital admissions
- Date of death

Primary outcomes included overall survival (OS) and peritoneal relapse-free survival (PRFS). Secondary outcomes included performance status as a surrogate for postoperative functional recovery. Survival outcomes were calculated from the date of surgery until the last follow-up or death.

Statistical Analysis

All statistical analyses were performed using IBM SPSS version 26. Continuous variables were reported as means

with standard deviations and compared using Student's t-test or Welch's t-test in cases of unequal variances, as determined by Levene's test.

Categorical variables were compared using Chi-square or Fisher's exact test. A two-tailed p-value of <0.05 was considered statistically significant. Confidence intervals (95%) were reported where appropriate.

RESULTS

A total of 100 patients with peritoneal carcinomatosis were included in the study, evenly divided between the two treatment groups: Cytoreductive Surgery alone (CRS Alone) and Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS+HIPEC), with 50 patients in each group.

Age and Peritoneal Carcinomatosis Index (PCI)

The mean age of patients in the CRS Alone group was 62.86 ± 7.48 years, while the CRS+HIPEC group had a mean age of 58.46 ± 8.13 years. The difference in age between the groups was not statistically significant ($p > 0.05$). Similarly, the mean Peritoneal Carcinomatosis Index (PCI) was 11.00 ± 3.12 in the CRS Alone group and 10.68 ± 3.44 in the CRS+HIPEC group, with no significant difference observed ($p > 0.05$).

Type of Surgery	Age (Mean \pm SD)	PCI Score (Mean \pm SD)
CRS Alone	62.86 ± 7.48	11.00 ± 3.12
CRS+HIPEC	58.46 ± 8.13	10.68 ± 3.44
Total	58.66 ± 7.77	10.94 ± 3.27

Sex Distribution

Both groups had near sex distributions. Females comprised 90% (n=45) of CRS alone while comprised 86% (n=43) in CRS+HIPEC, and male accounted

10% (n=5) in CRS alone while males accounted for 14% (n=7) in CRS+HIPEC, indicating no statistically significant difference in sex distribution between the two cohorts.

Sex	CRS Alone	CRS+HIPEC	Total
Female	45 (90.0%)	43 (86.0%)	86 (86.0%)
Male	5 (10.0%)	7 (14.0%)	14 (14.0%)
Total	50 (100%)	50 (100%)	100 (100%)

Primary Disease Type

The predominance of ovarian cancer cases in each group reflects the selection criteria applied to the collected data set (accounting for 68% of patients). Colonic cancer and

gastric cancer were each present in 12%, while appendiceal cancer was seen in 8% of patients. The distribution of disease types was identical between the two treatment groups, showing no significant variation.

Disease Type	CRS Alone	CRS+HIPEC	Total
Ovarian Cancer	34 (68.0%)	34 (68.0%)	68 (68.0%)
Colonic Cancer	6 (12.0%)	6 (12.0%)	12 (12.0%)
Gastric Cancer	6 (12.0%)	6 (12.0%)	12 (12.0%)
appendiceal Cancer	4 (8.0%)	4 (8.0%)	8 (8.0%)
Total	50 (100%)	50 (100%)	100 (100%)

Neoadjuvant Therapy

Neoadjuvant therapy was administered to 100% of patients in each group (n=50), This distribution was also

balanced across groups with no significant differences observed.

Neoadjuvant Therapy	CRS Alone	CRS+HIPEC	Total
Yes	50 (100%)	50 (100%)	100 (100%)
No	0 (0)	0 (0%)	0 (0%)
Total	50 (100%)	50 (100%)	100 (100%)

Overall Survival

Patients who underwent CRS+HIPEC had a significantly longer mean overall survival (37.90 ± 16.03 months) compared to those who underwent CRS alone (19.42 ± 8.45 months), with a mean difference of 18.48 months (95% CI: 3.38 to 13.58; $p = 0.001$). Levene’s test indicated unequal variances ($p < 0.001$), and the appropriate Welch's t-test was applied.

with a mean of 28.34 ± 13.32 months compared to 15.36 ± 5.58 months in the CRS group. The mean difference was 12.98 months (95% CI: 8.90 to 17.06; $p < 0.001$), also analyzed with Welch’s correction due to unequal variances.

Peritoneal Relapse-Free Survival

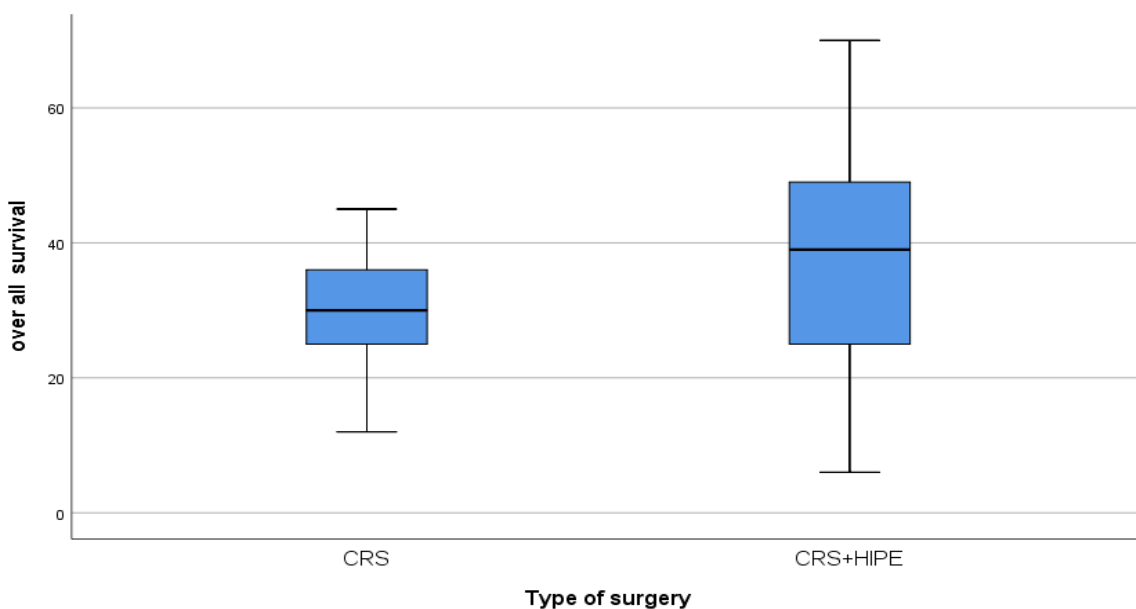
Similarly, the CRS+HIPEC group demonstrated significantly prolonged peritoneal relapse-free survival,

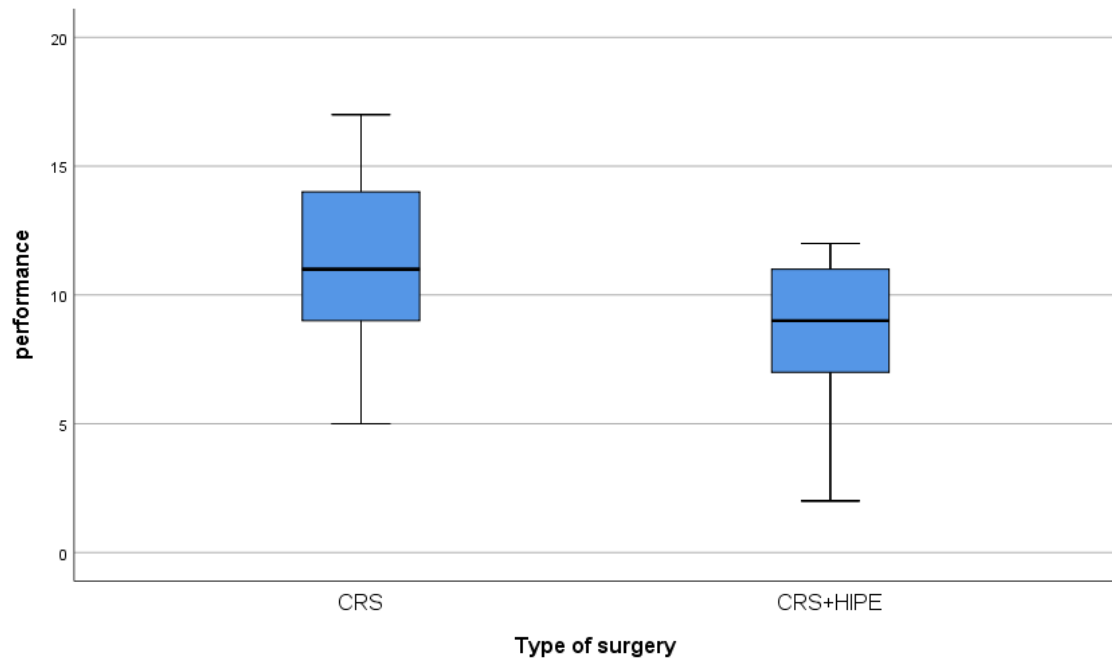
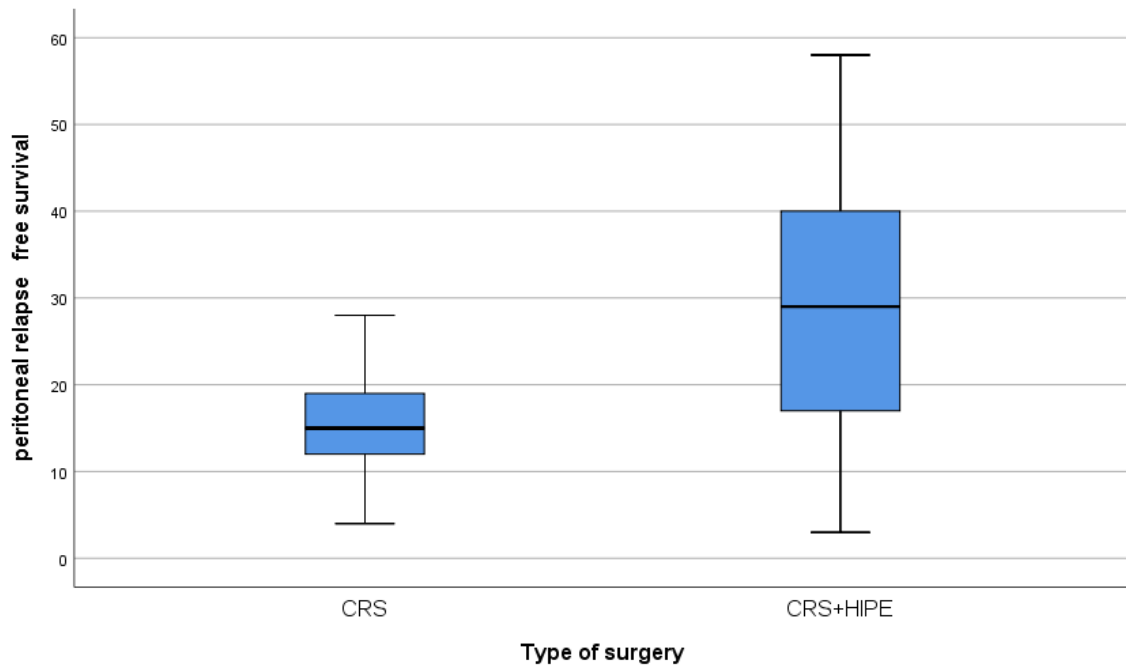
Performance Status

Performance scores were significantly better (lower) in the CRS+HIPEC group (8.58 ± 2.60) compared to the CRS group (11.06 ± 2.94), with a mean difference of 2.48 (95% CI: 1.38 to 3.58; $p < 0.001$). Equal variances were assumed for this comparison.

Outcome	CRS Mean \pm SD	CRS+HIPEC Mean \pm SD
Performance	11.06 ± 2.94	8.58 ± 2.60
Overall Survival (months)	19.42 ± 8.45	37.90 ± 16.03
Peritoneal Relapse-Free Survival (months)	15.36 ± 5.58	28.34 ± 13.32

Outcome	CRS (n = 50)	CRS+HIPEC (n = 50)	Mean Difference (95% CI)	p-value
Overall Survival (months)	19.42 ± 8.45	37.90 ± 16.03	18.48 (3.38 – 13.58)	<0.001
Peritoneal Relapse-Free Survival (months)	15.36 ± 5.58	28.34 ± 13.32	12.98 (8.90 – 17.06)	<0.001
Performance Score	11.06 ± 2.94	8.58 ± 2.60	2.48 (1.38 – 3.58)	<0.001





DISCUSSION

Our Iraqi cohort showed that adding HIPEC to complete Cytoreductive surgery achieved longer overall survival, a markedly longer peritoneal relapse-free interval, and better post-treatment functional scores than CRS alone, despite balanced baselines.

The direction and magnitude of benefit align closely with ovarian-predominant evidence: Aronson in the Netherlands^[7] confirmed durable 10-year gains in the final analysis, reinforcing that a carefully delivered oxaliplatin-based HIPEC can translate into sustained survival—not just earlier recurrence control.

External validity across disease phases is supported as well.

Classe in France^[8] demonstrated in the phase 3 trial that secondary CRS with HIPEC improved overall survival at the cost of higher grade ≥ 3 events—an efficacy–toxicity trade-off we should anticipate and manage within perioperative pathways.

Similar signals outside Europe strengthen generalizability: Lee in South Korea^[9] reported survival advantages with HIPEC when used at primary or interval cytoreduction, consistent with our ovarian-heavy case-mix.

Regimen selection matters for both efficacy and renal safety profiles.

Taliento in Italy^[10] synthesized randomized evidence and found that adding HIPEC at interval debulking after neoadjuvant chemotherapy significantly improves progression-free outcomes, while highlighting hematologic toxicity signals that justify standardized supportive care.

For colorectal peritoneal metastases, After complete CRS, Quénet in France found no survival benefit for a short (30-minute) oxaliplatin protocol, a cautionary note that shifted practice away from that regimen.

Contemporary consensus, however, supports a different approach: Hübner in Switzerland^[11] led the recommendations endorsing, in selected patients, oxaliplatin regimens with 90-minute exposure after complete CRS, while Cinquini in Italy^[12] coordinated a multi-society guideline emphasizing strict selection (low PCI) and procedural standardization.

Prophylactic or adjuvant strategies also show domain-specific benefits.

Arjona-Sánchez in Spain^[13] improved 3-year locoregional control with intraoperative HIPEC for cT4 colon cancer, and Hamm in the Netherlands^[14] showed in an individual-patient meta-analysis that right-sided disease may derive particular locoregional advantage—even as overall survival effects remain immature.

Our own superiority in overall and relapse-free survival therefore likely reflects ovarian predominance, disciplined cytoreduction, and avoidance of short-exposure oxaliplatin protocols—fully consistent with these updated positions.

Gastric cancer with peritoneal metastasis continues to be difficult, but contemporary data increasingly support benefit in highly selected patients. Chen in China^[15] pooled randomized trials and found improved 1- to 5-year survival and reduced recurrence with HIPEC, and Boshier in the UK^[16] corroborated survival signals across Intraperitoneal chemotherapy strategies in a comprehensive meta-analysis, while urging attention to heterogeneity and center effects.

Rau in Germany^[8] contributed important trial-level perspective by analyzing randomized data in gastric cancer, underscoring that outcomes hinge on exposure time, drug, and completeness of cytoreduction—elements our protocol already prioritizes.

Complementary practice-oriented syntheses such as Guchelaar in the Netherlands^[17] indicate that repeated intraperitoneal therapy can be delivered safely and may permit conversion surgery in a subset, reinforcing the

broader rationale for locoregional escalation in peritoneal disease biology.

Translationally, our better follow-up performance scores are consistent with data showing early quality-of-life dips after CRS±HIPEC with return to baseline by 3–6 months in randomized ovarian cohorts—an arc that fits what van Driel in the Netherlands^[6] and subsequent program reports have observed.

Program-building feasibility in complex multi-visceral settings is echoed by Dagenborg in Norway^[18], who showed that even combined liver resections with CRS-HIPEC can be delivered with acceptable morbidity in expert hands—an implementation signal directly relevant to national scale-up.

Taken together, our findings are congruent with what van Driel in the Netherlands^[6] and Aronson in the Netherlands^[7] established for interval debulking in ovarian cancer, they are compatible with selective colorectal indications when following Hübner in Switzerland^[10], Cinquini in Italy^[11], Arjona-Sánchez in Spain^[13], and Hamm in the Netherlands^[14], and they parallel the gastric signals summarized by Chen in China^[15], Boshier in the UK^[16], and Rau in Germany.^[8]

In Iraq's context—where Mahmood and his colleagues in Iraq^[19] has already documented early feasibility—the implication is clear: expand CRS+HIPEC access for carefully selected patients (particularly ovarian interval-debulking and low-PCI gastric cases), adopt mitomycin-based colorectal protocols with strict PCI and CC-0/1 requirements, and embed toxicity surveillance and prospective auditing as program capacity grows. This strategy operationalizes global evidence while honoring local realities, and it plausibly explains the superior survival and functional outcomes we observed.

LIMITATIONS

- This prospective, nonrandomized single-center study is susceptible to residual confounding and selection bias despite balanced baselines.
- Disease heterogeneity with an ovarian predominance limits generalizability and may inflate the apparent benefit.
- Future prospective, disease-specific studies are needed, incorporating:
 - Standardized HIPEC protocols.
 - Full morbidity reporting.

CONCLUSION

CRS+HIPEC should be scaled in Iraq for carefully selected patients—prioritizing interval debulking in ovarian cancer, MMC-based protocols for select colorectal cases after complete cytoreduction, and low-PCI gastric disease within structured pathways. Immediate steps are to standardize HIPEC parameters (agent, dose, temperature, duration), embed toxicity

surveillance, and launch a multicenter registry with time-to-event endpoints.

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