




## Gastrointestinal Cancer

# Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Gastric Cancer with Peritoneal Metastasis—Indian Experience

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South Asian J Cancer 2022;11(2):121–124.

## Abstract



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## Keywords

- ▶ cytoreductive surgery
- ▶ hyperthermic intraperitoneal chemotherapy
- ▶ gastric cancer
- ▶ peritoneal carcinomatosis
- ▶ palliative chemotherapy

**Introduction** Peritoneal metastasis secondary to gastric cancer is associated with poor prognosis. Recent studies have shown that cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) may be an efficacious treatment option for an otherwise palliative condition.

**Methods** A retrospective single institutional study of patients diagnosed with gastric carcinoma and peritoneal metastasis and treated with CRS and HIPEC from February 2015 to December 2019.

**Results** Sixteen patients with gastric cancer and peritoneal carcinomatosis were treated with CRS and HIPEC. Three patients underwent upfront surgery, and five patients underwent interval surgery. The mean peritoneal cancer index (PCI) was 3.5, and adequate complete cytoreduction (CC) score of 0/1 was achieved in all patients. All patients received HIPEC with mitomycin C. Major surgical complications were in 12.5% of patients. Grade I surgical site infection was present in one patient. Three patients had prolonged gastrointestinal (GI) recovery. The 30-day mortality was zero. Median follow-up time was 39 months. The median progression-free survival (PFS) was 12 months (95% confidence interval [CI] 6.86–17.13). The median overall survival (OS) was 17 months (95% CI 6.36–27.64).

**Conclusion** Multidisciplinary treatment of perioperative chemotherapy with CRS and HIPEC is a promising treatment option, which may prolong survival in selected patients, and large randomized clinical trials are warranted for it to become standard of care.

DOI <https://doi.org/10.1055/s-0041-1739176> ISSN 2278-330X

**How to cite this article:** SP S, Karivedu J, C RK, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Gastric Cancer with Peritoneal Metastasis—Indian Experience South Asian J Cancer 2022;11(2):121–124.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

We analyze the results of the treatment with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with gastric cancer and peritoneal carcinomatosis in Indian patients.

## Methods

This is a retrospective single institutional study of patients diagnosed with gastric carcinoma and peritoneal metastasis and treated with CRS and HIPEC from February 2015 to December 2019. All the patients with resectable peritoneal disease and no metastatic disease, Eastern Cooperative Oncology Group (ECOG) 0/1, < 70 years of age, and preoperative serum albumin > 3 g% were included in the study (–Table 1). To be considered for CRS and HIPEC, patients should have a normal organ function (serum creatinine < 1.5 × the upper limit of normal [ULN] or calculated creatinine clearance of ≥ 50 mL/min; bilirubin less than 1.5 mg/dL; hepatic enzymes < 3 times the ULN; white blood cell count ≥ 4,000/mm<sup>3</sup>; and platelet count ≥ 100,000/mm<sup>3</sup>). The patient cohort included cases undergoing upfront surgery, interval cytoreduction after neoadjuvant chemotherapy (NACT), and those undergoing surgery for recurrent disease. Patients with limited peritoneal dissemination (peritoneal cancer index [PCI] < 7) confirmed by laparoscopy or laparotomy were subjected to CRS/HIPEC. Patients with high disease burden and massive ascites were referred for NACT. Informed consent was obtained from all patients. Ethics committee (EC) approval and Institutional Review Board (IRB) approval was obtained. All patients were treated by a team of two surgeons, anesthesiologist,

intensivist, and medical oncologist having expertise in peritoneal surface malignancy. The extent of intraperitoneal tumor manifestation is determined using the PCI and a combined numerical score of lesion size (LS-0 to LS-3) and tumor localization (region 0–12).<sup>1</sup> The aim of CRS is to obtain optimal cytoreduction (defined as CCR-0/1) as a precondition for the application of HIPEC. Following cytoreduction, all patients underwent HIPEC by semiopen technique with a dedicated HIPEC machine (Rand Biotech) using injection mitomycin 35 mg/m<sup>2</sup>. Patient baseline demographics and perioperative details like PCI,<sup>2</sup> prior surgical score (PSS), the average blood loss, operative time, hospital stay, and ICU stay were recorded prospectively in all patients. Adverse events are graded according to common terminology criteria for adverse events (CTCAE). Clavien–Dindo classification was used to grade surgical complications. In-hospital mortality was recorded. Histopathology was assessed by dedicated oncopathologist. The patients were followed up with regular upper gastrointestinal (GI) endoscopy and radiological monitoring for any recurrence.

## Statistical Analysis

Continuous variables are presented as mean with standard error of the mean or median with range or interquartile range (IQR), as appropriate. Adverse events were recorded and graded according to the CTCAE version 4.0. Survival was calculated in a Kaplan–Meier survival curve. Progression-free survival (PFS) and overall survival (OS) both were calculated from date of surgery.

## Results

A total of 16 patients with gastric cancer and peritoneal carcinomatosis were operated from February 2015 to December 2019 at Manipal Comprehensive Cancer Center. The median age of our patients was 55.5 years. Prior surgical score was 0 for all 16 patients. Six patients underwent upfront CRS, while 10 patients underwent interval CRS after NACT. The mean number of cycles of NACT was 4.

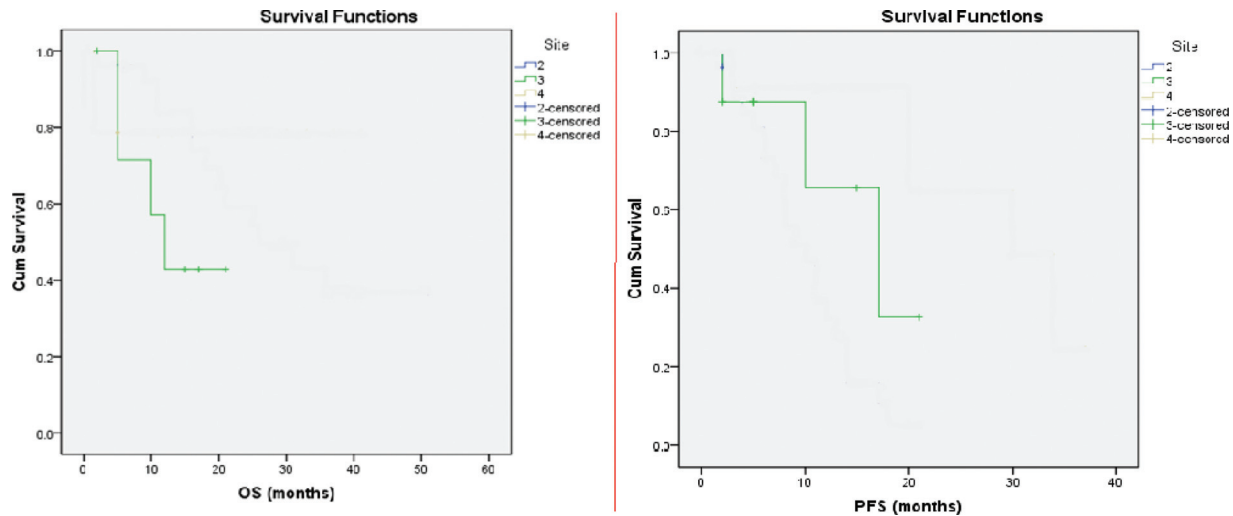
The mean PCI was 3.5 (range 1–7), and adequate complete cytoreduction (CC) score of 0/1 was achieved in all patients. The mean duration of surgery was 8.5 hours; mean intraoperative blood loss was 575 mL. Total gastrectomy and D2 lymphadenectomy were performed in all patients. Total peritonectomy was performed in two patients; pelvic peritonectomy was performed in 6 patients; and total omentectomy and lesser omentectomy were performed in all patients. Bilateral salpingo-oophorectomy was performed in two patients. Multivisceral resection (> 4 organs' resection) was done in one patient. All patients received HIPEC with 35 mg/m<sup>2</sup> of mitomycin C.

Seven patients were extubated in OT. Median intensive care stay was 2 days. Major surgical complications were observed in 2 patients (12.5%) who had major surgical site infections. Grade I surgical site infection was present in two patients. Six patients had prolonged GI recovery. The 30-day mortality was zero.

**Table 1** Perioperative patient characteristics

Variable	n
Age (years) median	55.5
Hemoglobin (g/dl) mean	11.5
Albumin (g/dl) mean	3.8
Performance status	
ECOG 0	12
ECOG 1	4
Comorbidity	4
Prior surgical score	
0	16
1	0
2	0
3	0
NACT	
Yes	6
Interval	10

Abbreviations: ECOG, Eastern Cooperative Oncological Group; NACT, neoadjuvant chemotherapy.



**Fig. 1** Overall survival (OS) curve and progression-free survival (PFS) curve.

Median follow-up time was 39 months. The median OS was 12 months (95% CI 6.86–17.13]. The median PFS was 17 months (95% CI 6.36–27.64) (->Fig. 1).

## Discussion

Systemic chemotherapy has improved the prognosis of patients with metastatic gastric cancer, reaching survival of 8 to 14 months in selected series.<sup>3</sup> However, the response rate of measurable gastric peritoneal carcinomatosis to systemic chemotherapy is only 14 to 25%, most likely attributable to poor penetration of systemic chemotherapy across the blood-peritoneal barrier.<sup>4</sup>

A meta-analysis by Yan et al<sup>5</sup> on adjuvant regional chemotherapy for resectable gastric cancer has shown a survival benefit from addition of intraperitoneal chemotherapy. A significant improvement in survival was associated with HIPEC (hazard ratio [HR]=0.60; 95% CI=0.43 to 0.83;  $p=0.002$ ) or HIPEC combined with early postoperative intraperitoneal chemotherapy (HR=0.45; 95% CI=0.29 to 0.68;  $p=0.0002$ ). They also noted that Intraperitoneal chemotherapy was also found to be associated with higher risks of intra-abdominal abscess (RR=2.37; 95% CI=1.32 to 4.26;  $p=0.003$ ) and neutropenia (RR=4.33; 95% CI=1.49 to 12.61;  $p=0.007$ ).

A recent randomized control trial by Rudloff et al<sup>7</sup> comparing CRS-HIPEC with systemic chemotherapy demonstrated an overall survival of 11.3 months in CRS-HIPEC arm versus 4.3 months in the chemotherapy alone arm.

Despite several studies reporting encouraging survival results with CRS + HIPEC in patients with gastric cancer and peritoneal carcinomatosis,<sup>3,8-10</sup> its use has not been standardized. PCI and CC scores are known to be independent prognostic factors after CRS plus perioperative chemotherapy.

From a systematic review and meta-analysis of data from 748 patients with peritoneal metastasis, Coccolini et al<sup>11</sup> concluded that the PCI cutoff level can be 12 for better or worse prognosis. Accordingly, peritonectomy and CRS are not

recommended in patients with PCI higher than the cut-off level. Yonemura et al<sup>12</sup> could show in a multivariate analysis that the completeness of cytoreduction is a highly significant factor for the prediction of patient survival. He also determined that the best results are obtained with PCI < 6.

The optimal cytoreduction, measured as CC score showed a survival benefit, according to a systematic review by Coccolini et al. The OS increased by CC0-CC1 cytoreduction in patients with peritoneal carcinomatosis of gastric origin.

Our study results, despite limited number of patients with a mean follow-up of 38 months, show recurrence-free and OS rates comparable with earlier published studies. Mean PCI of our study was 3.5, which is a good prognostic factor, and optimal cytoreduction (CC score 0/1) that we were able to achieve in all our patients may have contributed to this.

Therefore, the use of CRS-HIPEC for selected patients with gastric cancer and peritoneal carcinomatosis seems to improve survival, as evidenced by other systematic reviews.<sup>13</sup> Although the survival benefit is less encouraging than those obtained for other peritoneal surface malignancies, a multidisciplinary approach for physically fit, low burden disease with complete cytoreduction can be benefited.

## Conclusion

Multidisciplinary treatment of perioperative chemotherapy with CRS and HIPEC is a promising treatment option, which may prolong survival in selected patients (low peritoneal disease burden, physically fit patients) with gastric carcinomatosis. Large randomized clinical trials are warranted to prove its efficacy and become a standard of care.

### Funding

The authors declare that they have not received any funding.

### Conflict of Interests

The authors declare that they have no competing interests.

### Acknowledgment

Dr. Arun Kumar, Consultant Biostatistician, for statistical analysis and sample size calculation.

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