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Peritoneal metastasis in gastric cancer: Mechanisms and management strategies

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ABSTRACT

Background: Surgical trauma or full-thickness invasion of gastrointestinal cancer through the gut wall might cause peritoneal surface malignancy.

Objective: This research examined the mechanisms and treatment options for Peritoneal Metastases (PM) in gastric cancer.

Material and Methods: Using data on cancer and demographics from the National Cancer Centre (NCC) in India for 2016, PM prevalence in 2020 was projected. Gastric Cancer (GC), which ranks third in terms of frequency, has a 25% 5-year survival rate. This is a result of PM. Palliative Systemic Chemotherapy (SCT) should be given to PM-GC for six months. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Cytoreductive Surgery (CRS) are popular peritoneal carcinoma treatments in 2016. Survival of GC with PM is improved by CRS and HIPEC. In patients with locally advanced GC who do not have macroscopic PM, HIPEC, and other intraperitoneal therapies can prevent peritoneal recurrences. Laparoscopic HIPEC and NIPS minimize peritoneal disease and promote cytoreduction.

Results: In India gastric cancer PM rates: 523,937 instances, PM 371.0 per million. India needs 1194 specialized PM treatment centres to treat 365 high-quality patients annually. India has 1580 top-tier tertiary hospitals. Since this is the case, India should have at least 2 PM treatment centres open for every 3 first-rate tertiary hospitals.

Conclusion: A large number of people with PM in India demand further investment in the country's limited network of specialized PM treatment institutions. Finally, Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) or laparoscopic HIPEC can manage malignant ascites symptoms in individuals with the high-volume peritoneal illness.

Keywords: Peritoneal Metastasis (PM), Gastric Cancer (GC), Systemic Chemo Therapy (STC), Cytoreductive Surgery (CRS), Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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INTRODUCTION

In the last 40 years, GC which accounts for 10% of all malignancies worldwide has slipped from its previous position as the most frequent malignancy. Despite this adjustment, it continues to rank third among cancer-related causes of mortality [1]. PM is rare across all cancers that might proceed to carcinomatosis. Over 75,000 people get PM annually. Appendix, ovarian, and peritoneal cancers often metastasize in the PM pattern. Despite initial lung tumours, breast cancer, skin cancer, and soft tissue sarcoma, gastrointestinal malignancies have a moderate PM risk. In theory, peritoneal metastases develop when tumour cells are secreted directly into the peritoneal space, where they can implant on peritoneal surfaces, expand due to the development of new vascular networks, and eventually metastasize to other peritoneal surfaces and abdominal organs. Some tumours can spread to the organs beneath the surface [2]. PM is rare across the full spectrum of cancers that might proceed to carcinomatosis. PM affects around 75,000 persons annually. Tumours from the appendix, ovaries, and peritoneum often metastasize in the PM pattern. Gastrointestinal tumour patients have a modest PM risk, unlike those with soft tissue sarcoma, breast cancer, skin cancer, and primary lung tumours. A significant quantity of ascites and a clear thickening of the parietal peritoneum are the traditional CT criteria for PM. However, the majority of these symptoms typically show up in late-stage PM. Figure 1 depicts the general structure of gastric cancer. Thus, CT detection of PM has good specificity but low sensitivity (50%). Clinical practice is affected: Occult PM occurred in 10%–30% of advanced gastric cancer patients with negative CT diagnosis for PM [3]. Cancer patients from a variety of backgrounds frequently experience tumour spread to the peritoneum. Ovarian cancer patients have PM at diagnosis 75% of the time, gastric cancer 17%, and colorectal cancer 10%. Only palliative surgery and systemic chemotherapy have been used to treat PM. PM causes human suffering and high healthcare expenses. Gastric-based PM patients had median survival duration of 1 months-3 months, while colorectal-based PM patients lived up to 12.7 months. Over the past 25 years, late-stage ovarian cancer patients' 10-year survival rate has not altered despite new treatment options [4].

Individuals with a diffuse subtype of gastric cancer were more likely to have peritoneal metastases (80%) than those with an intestinal subtype (40%). Additional risk factors have been discussed, including lymph node positivity, signet ring cell

malignancy, serosa invasion, and undifferentiated grading. For stomach cancer peritoneal metastases, the NCCN recommends palliative systemic chemotherapy and/or appropriate supportive care. The recent development of multimodal treatment modalities like CRS and HIPEC has increased overall survival in a group of patients. These treatments were found to be effective in treating individuals with peritoneal metastases from gastric cancers [5]. The research gives mechanistic insights that have the potential to be turned into effective targeted therapy for patients who have peritoneal metastases as a result of Pancreatic Ductal Adenocarcinoma (PDA) [6]. Activatable theragnostic devices have the potential to greatly improve cancer diagnosis and treatment because of their high detection specificities, efficient ablative capabilities, and low unwanted effects. To effectively diagnose and treat peritoneal metastases, the research group developed a NIR-II nanotheranostic system (FEAD1) that is activated by the tumour microenvironment (TME) [7]. Study described an original organic NIR-II dye called H10 that utilizes a "Selenadiazolo-[3,4-f]-benzo-[c]-[1,2,5]-Thiadiazol (ST)" dependent architectural component and possesses exceptional Aggregation-Induced-Emission (AIE) properties [8]. These qualities include an I/I0 value that is more than 1.6. Ovarian cancer patients will have a much better chance of survival as a result of this innovative approach; it will result in the creation of cutting-edge equipment for early diagnosis. When stomach cancer spreads to the peritoneum, it is fatal. PM of GC is now viewed as incurable because the molecular pathway is not well understood. Therefore, the study used bioinformatics to analyse gastric cancer peritoneal metastasis to understand pathophysiology and aid focus therapy [9]. Here in is detailed a simple procedure for fabricating a novel "NIR-II nanoprobe (APP-Ag2S-RGD)" in the form of a chain. The "NIR-II Ag2S QDs and RGD peptide" that targets tumours are first chemically cross-linked [10]. The research used CRS and HIPEC with Oxaliplatin (OX) in patients with colorectal PM is developing [11]. PIPAC is a new strategy that has positive outcomes for individuals with PM. Study determined the postoperative prognosis and survival of patients with unrespectable PM of gastric origin treated with chemotherapy and PIPAC [12]. The research goal was to evaluate the survival benefit of routinely combining HIPEC with observation and second opinion surgery in patients who are at high risk of developing colorectal peritoneal metastases [13]. Employing limited and imbalanced samples of Computed Tomography (CT) images, the article employed an arbitrary extension approach to develop and refine a radionics-based neural network algorithm to forecast PM in patients with GC [14]. Study discussed the composition and shape of the Tumour Micro Environment (TME) in colorectal PM and how these findings might be applied to new treatments intended to re-engineer the stoma's metastasis-promoting activities [15]. The study determined the prevalence, course of care, and survival trends among Dutch patients with synchronous PM for GC [16]. A study examined whether receiving CRS alone or in combination with HIPEC resulted in any additional advantages [17]. The following steps must be done after a PM diagnosis: consult a Multidisciplinary Coordination Meeting (MCM) that specializes in abdominal illness for advice; on the recommendation of the MCM, transfer the individual in question to a reference facility with HIPEC competence [18]. According to research, colon cancer cells are proliferated, migrated, and invaded by Cancer-Associated Fibroblasts (CAFs), which up-regulate CPT1A to actively oxidize FAs and undergo minimal glycolysis [19]. These three procedures are promoted in this way by CAFs. Peritoneal Mesothelial Cells (MCs) can take up the PKH26-labeled exosomes of Gastric Cancer (GC) cells, according to the study, which examined the migration of GC cells [20]. Following a rescue experiment in miR-106a-enriched GC-expos, the MCs become viable again, apoptosis is reduced, and Smad7 expression is examined. The purpose of this study is to modify, based on experience, the mechanism of action and treatment of PM with a GC lineage in a variety of scientific circumstances.

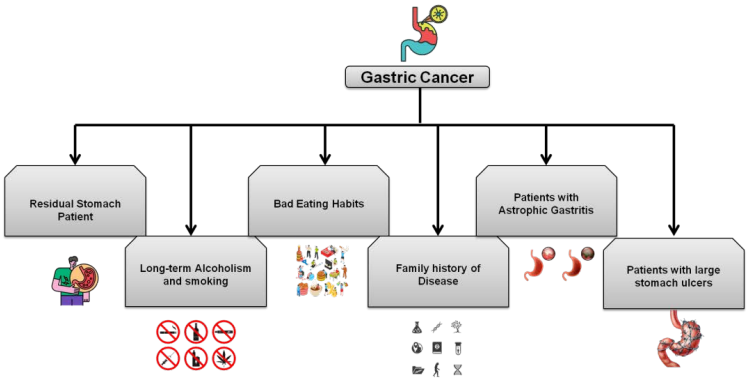

Fig. 1. General structure of gastric cancer

MATERIALS AND METHODS

Peritoneal metastasis is the term for the process by which cancer cells spread from their initial site to the thin layer of tissue that lines and covers the abdomen's organs. Regular check-ups with medical professionals are crucial for cancer patients to track the disease's development and catch any early indications of peritoneal metastasis. The likelihood that this condition can be successfully managed can be increased by early identification and treatment.

Patient's data collection

The most recent cancer statistics from the National Cancer Centre in India were issued in 2016; it allowed us to estimate the prevalence of common PM using epidemiological data on stomach cancer in the population. Most PM patients in India had palliative chemotherapy and/or simple debulking surgery due to a lack of CRS+ HIPEC facilities. To better reflect PM patients' diagnosis, prognosis, and status in India, we used information on patient survival and demise from solely chemotherapy and/or surgery. The annual mortality rates of PM patients were calculated using information from extensive clinical research. Patients who passed away while being observed were removed from the yearly group.

Mechanisms of PM from GC

Clinicians still face challenges while attempting to treat PM in patients with stomach cancer. Therefore, it is crucial to investigate the root causes of PM to create effective treatments and improve the prognoses of GC patients. The "seed-and-soil" idea, which dates back 126 years, has not led to sufficient knowledge of the processes driving organ-specific metastasis. The cancer cells in the liver are like seeds, and the optimum environment in metastatic sites is like fertile soil, in this metaphor.

Multiple sequential mechanisms aid in the formation of PM of GC, as proposed "seed and soil" theory. Tumour growth includes serous layer invasion, separation from initial sites, seeding and survival in the cavum abdominis, adherence to the peritoneum, basement membrane invasion into sub peritoneal tissue, and proliferation with blood vessel neogenesis. Epithelial-Mesenchymal Transition (EMT), angiogenesis, cell migration, adhesion, and invasion characterize gastric cancer's Primary Metastatic (PM) stage. There are a lot of substances and signalling pathways involved in this procedure. The overall expression profile (21168 genes) was analysed for two cell lines, one derived from primary GC and the other from a metastatic tumour of the cavum abdominis. EMT, caused by a decrease in E-cadherin expression, also contributes to gastric cancer. GC-derived exosomes disrupted the mesothelial barrier to create PM, demonstrating their significance in premetastatic environment remodelling. This revealed the GC PM mechanism. Based on their examination of 5 GC cases with mesentery spread of the small intestine, they hypothesized that hematogenous metastasis may be peritoneal implantation. It is still not clear what processes underlie the expansion of PM of GC shown in Figure 2.

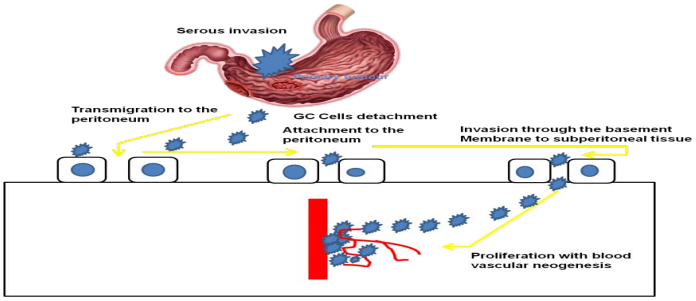

Fig. 2. Mechanism of the PM from GC

Value of peritoneal cancer area

The Peritoneal Cancer Area (PCA) helps determine the degree and spread of cancer in the peritoneal cavity, which houses the abdominal organs. Peritoneal cancer begins in the thin tissue that borders the belly and covers the abdominal organs. Cancer from the ovaries, colon, or stomach can potentially cause it. CT, MRI, and PET scans measure PCA to stage peritoneal cancer. Higher PCAs indicate advanced cancer and a higher likelihood of recurrence following treatment. PCA can track peritoneal cancer treatment efficacy. An increase in PCA may suggest that cancer has advanced or recurred, whereas a decrease may indicate that treatment has worked. PCA can assist diagnose, stage, and treat peritoneal cancer by revealing cancer's extent and dissemination in the peritoneal cavity. Due to the interconnected nature of PCI and CCS, a PCI evaluation is necessary for the selection of patients to undergo CRS with HIPEC.

Preoperative and postoperative SCT

The periods of universal chemotherapy for a surgical procedure are denoted to as preoperative and postoperative chemotherapy. Preoperative systemic chemotherapy is managed before surgery and is frequently employed to decrease a tumour's development and assist to eliminate it more effortlessly. By decreasing the probability of cancer reappearance subsequent surgery, this strategy, which is often active in tumour that have evaporation to other portions of the body, might assist to advance the patient's findings.

Postoperative systemic chemotherapy is managed subsequent surgery and is frequently employed to eliminate any cancer cells that could have analysed the process. The patient's overall survival proportion might be increased and the hazard of cancer recurrence could be eliminated with the assist of this technology. Preoperative, postoperative, or a mix of preoperative and postoperative systemic chemotherapy depends on the cancer type, stage, patient status, and other factors. Usually, the patient's healthcare professional decides when and how long to administer chemotherapy and these parameters may change depending on the patient's reaction to the treatment. Treat localized; potentially respectable peritoneal illness multimodal. Chemotherapy before and after surgery is ideal. Non-metastatic people are treated with three ECF/ECX (epirubicin, cisplatin, fluorouracil, or capecitabine) treatments both prior to and following operation. Since FLOT has a better survival proportion, it is preferred for treating limited tumours with intraperitoneal illness and other distant areas. FLOT entails 4 prior and 4 postnatal sessions.

Neoadjuvant Intraperitoneal Chemotherapy (NIPEC)

NIPEC is a method of treating some types of cancer that includes injecting chemotherapy medications right into the abdominal cavity before surgery. NIPEC shrinks the tumour and kills any peritoneal cancer cells. Advanced gastric cancer, ovarian cancer, and other gastrointestinal malignancies are frequently treated with NIPEC. It is frequently given in conjunction with surgery, systemic chemotherapy, and other forms of treatment to make them more effective. During surgery, a catheter is placed into the abdominal cavity to provide NIPEC; alternatively, an abdominal port may be implanted. After being infused into the abdomen for a while, the chemotherapy medications are subsequently drained out. NIPEC is another action, is being tested in clinical studies. It is crucial to go over the potential advantages and disadvantages of NIPEC with your medical team before deciding if it is the best course of action for your particular case.

CRS with HIPEC

Cancers that have progressed to the peritoneal cavity may respond to CRS and HIPEC. A visible tumour in the peritoneal cavity is first removed by the surgeon during the surgery. Then, for some time, often around 90 minutes, a heated solution containing chemotherapy medications is circulated in the abdomen. Killing any cancer cells that may still be present but are not readily apparent to the surgeon is the aim. In contrast to conventional chemotherapy, HIPEC often uses a separate set of chemotherapy medications. Higher doses can be utilized without having as many negative effects because the medications are just administered to the affected location and not circulated throughout the body. A highly qualified surgical team is needed for the difficult surgery of CRS with HIPEC. It might be applied as a stand-alone therapy for specific tumours or as a component of a multimodal strategy that also uses chemotherapy, radiation, and/or targeted therapy. CRS with HIPEC's suitability depends on the patient's health, cancer type and stage, and other factors. Table 1 depicts the HIPEC as a treatment for PM from GC.

Tab. 1. HIPEC as treatment of PM from GC

The overall count of patients	Drug	Morbidity	Survival	Ref
97 (CRS) *vs.* 180 (CRS + HIPEC)	Oxaliplatin, MMC, and Cisplatin	7.4% *vs.* 10.1% of people die 53.7% *vs.* 55.3%.	18.8 *vs.* 12.1 months for the median OS. 19.9% over five years against 6.4%	[21]
(CRS + HIPEC) 235	Oxaliplatin, MMC, Cisplatin, and Doxorubicin	D-C in grades III–IV: 17% Death rate: 5.1%	OS: 13 months on average 5 year OS: 6%	[22]
(CRS + HIPEC) 88	Doxorubicin, MMC, Oxaliplatin, and Cisplatin	31% in grades III–IV D–C Death rate: 3.4%	OS: 21.2 months on average 3.0 OS: 30.9%	[23]

The primary prerequisite to increase survival time is full cytoreduction. The CRS should only be performed at specialized hospitals that have shown prior success in diagnosing and treating peritoneal illnesses. D2 lymphadenectomy, Gastrectomy, and removal of any peritoneal implants are performed by CRS to eradicate the illness. Sugar baker elaborated on how peritonectomy is performed. Their expert execution is required to successfully finish these intricate processes. The surgeon can get rid of the visible disease, but the microscopic disease that's left behind is likely to create recurrences. HIPEC takes advantage of the synergy and effect of heat in combination with strong cytostatic dosages working locally to eradicate this microscopic disease.

Prophylactic or adjuvant HIPEC

When used to treat certain types of cancer, prophylactic or adjuvant hyperthermic intraperitoneal chemotherapy, or HIPEC, involves injecting hot chemotherapy medications directly into the abdominal cavity during or after surgery. To eliminate any potential cancer cells that may be in the abdominal cavity but are too small to be noticed, prophylactic HIPEC is administered during surgery. This is done to increase long-term survival and lower the likelihood of cancer recurrence. Contrarily, adjuvant HIPEC is administered following surgery to treat any cancer cells that might not have been completely eradicated during surgery. This is done to raise the likelihood of a cure and lower the danger of a cancer recurrence. Advanced ovarian cancer, appendiceal carcinoma, and peritoneal mesothelioma are frequently treated with HIPEC. It is typically given along with cytoreductive surgery, which entails getting rid of the entire visible tumour. The hot chemotherapeutic chemicals are circulated throughout the belly for a while during the HIPEC treatment, often lasting between 30 minutes and several hours. The chemotherapy medications' efficiency and capacity to enter cancer cells are improved by the use of heat. After major surgery, peritoneal relapse is the most common recurrence site for locally progressed GC. When used in conjunction with a curative gastrectomy, HIPEC can prevent peritoneal recurrence in individuals without PM who have locally advanced GC. HIPEC can be used as a preventative measure for the lack of PM shows as the Table 2.

Tab. 2. HIPEC as a preventative measure in the lack of PM

Number of patients	Drug	Morbidity	Survival	Ref.
125(CRS + HIPEC)	CDDP + MMC CDDP + DOC LP + DOC	29.6%, 39.2%, 31.2%	5 year OS: 43.8%, 24.7%, 18.6%, and 15.7%,	[24]
154 (surgery + HIPEC) 76 *vs.* 78 (surgery alone)	Cisplatin + Doxorubicin	76.4% *vs.* 52.9% 12.8% *vs.* 27.6%	3 year progression-free survival was 47%	[25]
50 (surgery + HIPEC)	Cisplatin + Oxaliplatin	Improved rate of morbidity in the postoperative	3 year 84.8 and 88.2%	[26]
1376 (CRS + HIPEC)	MMC, CDDP, OHP	The HIPEC+CRS group has a greater chance	5 year 86.9%, 70.5%, 63.7% and 55.7%	[27]
2000 (surgery + HIPEC)	Epirubicin, Cisplatin, and Fluorouracil/ Capecitabine (ECF/ ECX)	36% *vs.* 27% 30% *vs.* 19%	OS: 72%	[28]
58 (surgery + HIPEC) *vs.* 33 (surgery alone)	MMC+ Cisplatin	26.6% *vs.* 50.9% 6.5%–39.9%	5-year overall survival (OS) estimates were 69% and 58%	[29]

Palliative treatment

When a patient has a serious condition, such as cancer, heart failure, or dementia, palliative care is a type of medical care that focuses on reducing their symptoms and enhancing their quality of life. Palliative care aims to control a patient's discomfort, elevate their morale, and attend to any other physical, emotional, or spiritual needs they may have. Palliative care can involve a range of different therapies, including drugs to treat symptoms and control pain, physical therapy to increase mobility, counselling to address patients' emotional and psychological needs, and spiritual assistance to help them find meaning and purpose in life. Several locations, including hospitals, nursing homes, hospices, and patients' homes, can offer palliative care. It is crucial to understand that hospice care, which is a form of palliative care frequently provided to patients with a life expectancy of six months or fewer who are no longer receiving curative therapy, is distinct from palliative treatment. However, palliative care is provided regardless of the severity of an illness and is often provided in tandem with curative treatment. Malignant ascites, manifesting as fatigue, early satiety, dyspnoea, and abdominal pain, is a common complication in patients with GC who have an unrespectable PM. For these patients, laparoscopic HIPEC is a possibility. 95% success rates in symptom control have been recorded in several studies. A high-pressure injector is used to aerosolize the medication during laparoscopy, allowing for greater tissue penetration.

RESULTS

Gastric cancer, also known as stomach cancer, occurs when malignant cells form in the stomach lining. It is the third biggest cause of cancer-related fatalities and the fifth most prevalent cancer in the world. Typically, surgery, chemotherapy, and/or radiation therapy are used to treat stomach cancer. The type of treatment is determined by the cancer's stage, location, and general health of the patient.

Incidence for GC-PM in India

The National Cancer Centre in India estimates that 679,100 new cases of GC were diagnosed in the country in 2015. GC PM has a 43% chance of occurring, according to epidemiological studies. Thus, approximately 292,013 new GC PM Patients were added per year. Using 2015's total population of 1383.26 million, the statistical year book India 2021 calculated a GC PM Incidence rate for India of approximately 211.1/million.

Patients with GC-PM have a very poor likelihood of surviving three decades following therapy, and the majority of survivors pass away in the initial year of therapy, based on survival proportion assessments that have been reported. Patients with GC-PM were followed for a total of 3 years, which corresponds to the duration required for clinical treatment. Using an incidence rate of 211.1 per 1,000,000 people, the prevalence of GC PM in India is shown in table 3. The number of people with GC PM in 2020 is projected to be 523,937, with a prevalence of 371.0 per one million.

Tab. 3. Calculating the frequency of GC-PM

Year	2020	2019	2018	2017
3 years (-90%)	29,810	29,767	29,668	29,554
2 years (-82%)	53,658	53,580	53,403	53,197
1 year (-52%)	1,43,088	1,42,881	1,42,407	1,41,859
New cases of GC-PM patients	2,98,099	2,97,668	2,96,682	2,95,540
Incidences	371.0/million			
The total number of patients	5,23,937			

Figure 3 depicts the overall survival of GC-PM patients. In cases of gastric cancer, PM denotes the spread of cancerous cells from the stomach to the lining of the abdominal cavity or peritoneum. Gastric cancer metastases frequently take the form of PM, which has a dismal prognosis. A typical PM with stomach cancer is a difficult condition to treat, and the outlook is frequently dismal. Early detection and intensive treatment, however, can increase the likelihood of survival and possibly lengthen the patient's life.

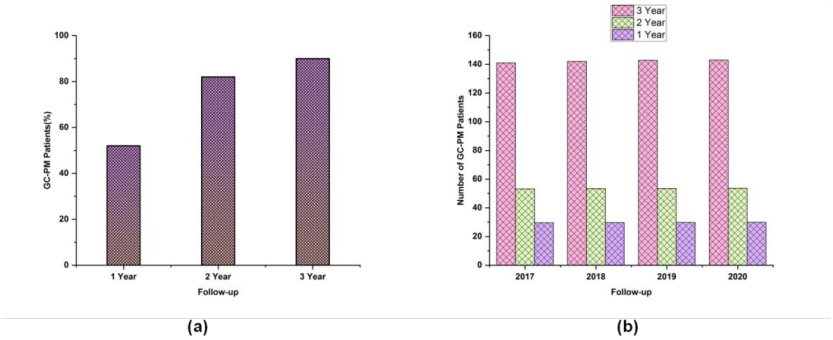

Fig. 3. Overall survival of GC-PM patients

Figure 4 depicts the proportion survival of the PM. We previously reported on our experience with CS/HIPEC operations for patients with GC-PM for 15 years. As a result, gastric (35%), 29% of peritoneal mesothelioma, 10% of ovarian, 9% of colorectal, and 6% of Pseudomyxoma peritoneal. The average time of completion was 560 minutes. 59% of patients had complete cytoreduction. 3 year and 5 year survival rates were 40.0% and 27.8% respectively; the median Overall Survival (OS) was 22.2 months. Gastric cancer had the longest median OS at 63.5 months, followed by ovarian cancer at 28.5 months, mesothelioma at 27.1 months, and colorectal cancer at 16.4 months, and Pseudomyxoma peritoneum at 6.1 months.

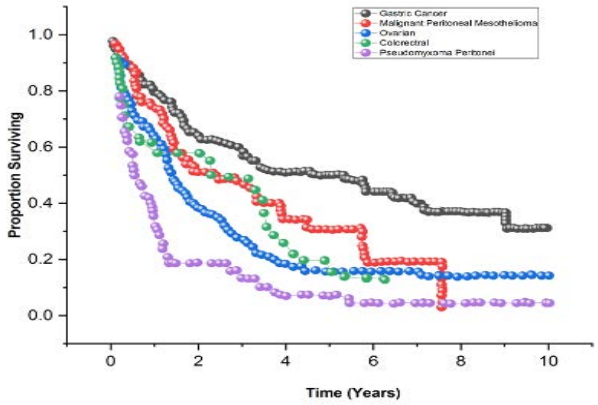

Fig. 4. Proportion survival of the PM

Figure 5 depicts the Survival probability of CRS with HIPEC. The average time patients were followed up was 33 months. Patients who had HIPEC combination chemotherapy had a median OS of 15.9 months, compared to just 10.8 months for people in the CRS group. The HIPEC and CRS groups had three-year survival rates of 18.4% and 10.1%, respectively. Additionally, we found that the 3-year OS rate was 27.0% and that the median Overall Survival time (OS) for patients who received palliative gastrectomy plus HIPEC plus chemotherapy was 20.8 months.

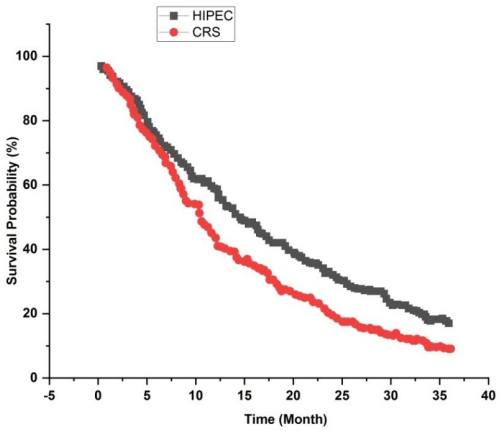

Fig. 5. Survival probability of CRS with HIPEC

DISCUSSION

The prospects of the PM from GC succeeding are slim. The identification of patients who might benefit from a multimodal treatment, patients should be managed in centres with experience. To diagnose the condition and acquire cytology, a diagnostic laparoscopy is required. CRS with HIPEC and intensive neoadjuvant chemotherapy may improve individuals with low levels of PM and single positive cytology. Locally advanced GC increases the chance of peritoneal recurrence. High-volume PM reduces patient quality of life. Palliative care patients may benefit from laparoscopic HIPEC or PIPAC. India faces a serious problem with Particulate Matter (PM), and the current network of specialized PM treatment facilities is struggling to meet the country's growing demand. There is additional work to be done on encouraging the establishment of particular PM behaviour that employ CRS+HIPEC as their primary method of care.

CONCLUSIONS

These clinical circumstances may require rethinking advanced GC treatment. The management of PM of GC remains difficult despite substantial advances in pathophysiology, treatment, and therapy. Several hurdles must be overcome before routine use of genetic identification for free tumour cells is possible; moving forward, larger-scale future clinical investigations focusing on GC patients in need of PM conversion treatment. The timing, technique, and indications of conversion therapy, among other important issues, are still unclear.

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