An In-Depth Look at Cytoreductive Surgery Paired with Hyperthermic Intraperitoneal Chemotherapy

By: Alexandra Susan Lee

A Thesis submitted to the Department of Biology in partial fulfillment of the requirements for the degree of Bachelor of Science

Academic Advisor: Dr. Jennie Carr

Date: 18 April 2020

Washington College Honor Code: I pledge my word of honor that I have abided by the Washington College Honor Code while completing this assignment.

Thesis Advisor: Dr. Martin Connaughton

TABLE OF CONTENTS

ABSTRACT

Cytoreductive surgery paired with hyperthermic intraperitoneal chemotherapy is a relatively novel technique used to treat various forms of cancer, including ovarian cancer, gastric adenocarcinoma, and peritoneal carcinomatosis. Cytoreductive surgery is performed by surgically removing visible tumor nodules in the peritoneal cavity. Hyperthermic chemotherapy is then locally administered to the surgical region. The use of hyperthermia increases the toxicity of the applied chemotherapy agent by promoting DNA-crosslinking and tumor infiltration and leads to destruction of cancer cells through protein denaturation and activation of apoptosis. Three primary articles were used to highlight the varying protocols of this novel procedure, including classification of resection status after cytoreductive surgery and temperature of the applied chemotherapy agents. Additionally, overall survival rates of patients who received cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy were compared and analyzed against patients who received systemic chemotherapy as treatment. Overall, it was shown that the novel treatment should only be utilized under stringent patient selection processes due to the intensity of the treatment and complications that can arise.

INTRODUCTION

Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is an aggressive treatment for peritoneal carcinomatosis that is restricted to a single area of the body (Smith & Nathan, 2019). The overall process begins with a surgeon cutting out macroscopic aspects of the malignant tumors that have metastasized, followed by distribution and infusion of heated chemotherapy into the abdominal cavity (Smith & Nathan, 2019). This process is also colloquially known as 'shake and bake' since the patient is sometimes jostled to evenly distribute the chemotherapy into the abdominal cavity. The localization of the heated chemotherapy grants respite for the rest of the body since the toxin is not injected into the bloodstream, just directly into the abdominal cavity. In addition, the use of heated chemotherapy brings about hyperthermia within the cells of the cavity, allowing for a greater number of malignant tumor cells to be destroyed (Smith & Nathan, 2019).

Before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were performed together as one treatment, CRS was used as one of the treatments for ovarian cancer and peritoneal carcinomatosis. When performing CRS, the overarching goal is to surgically remove the macroscopic portions of the disease (Mehta et al., 2016). The entire process of cytoreductive surgery can include a wide range of procedures that can range from removing one nodule to resection of the entire peritoneal cavity (Smith & Nathan, 2019). In most cases, CRS was followed by systemic chemotherapy treatments through the blood. After the 1930s, the use of intraperitoneal chemotherapy shifted from standard use to use of heated chemotherapy for the purpose of increasing the potency and efficacy of the chemotherapy agents (Neuwirth et al., 2015). In the 1960s, physicians E.W. Munnell and C. Griffiths conducted studies that showed that Stage IV ovarian cancer patients had increased survival numbers when aggressive cytoreductive surgery was performed to reduce tumor sizes to less than 2cm (Neuwirth et al.,

2015). Years later, physician J.M Larkin reported that regular systemic chemotherapy reduced the negative effects of tumors on the body, which then lead to the use of specific targeted chemotherapy agents for aggressive cancers in the 1980s (Neuwirth et al., 2015). Around the same time period, physician P.H. Sugarbaker developed an advanced approach to CRS that could apply to peritoneal carcinomatosis of differing causes and used peritonectomy (removing cancerous linings of abdominal cavity) combined with intraperitoneal chemotherapy; Sugarbaker formally developed the technique in 1995 (Neuwirth et al., 2015). Today, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is used in hospitals located in the United States, Europe, and Japan, with expansion occurring as the treatment becomes more mainstream (Glockzin et al., 2009).

Overall, the advantages of HIPEC over post-operative intraperitoneal chemotherapy are extensive. The intraoperative distribution of the heated chemotherapy allows for the drug to make direct contact with the malignancies rather than affect unnecessary lesions associated with post-operation (Cowan et al., 2017). Additionally, the chemotherapy is able to be pumped into the area of interest under controlled conditions rather than distributing the drug throughout the blood stream (Cowan et al., 2017). Lastly, the heated chemotherapy agents (rather than non-heated chemotherapy agents) increases the toxicity of the agent by promoting DNA-crosslinking and tumor infiltration (Cowan et al., 2017). Hyperthermic conditions of the chemotherapy agents ultimately leads to toxic effects on the cancer cells through protein denaturation and activation of apoptosis, also known as cell-death (Glockzin et al., 2009).

Some literature suggests that the optimal hyperthermic conditions for HIPEC include applying chemotherapy at temperatures ranging from 41°C to 42°C (Verwaal et al., 2003), with other literature reporting temperature ranges of 42°C to 45°C (Cowan et al., 2017). However, some researchers state that bowel perforation can occur if the temperature of the intraabdominal

cavity exceeds 43°C (Montori et al., 2014). Cowan et al. (2017) states that initial trials of CRS followed by HIPEC showed that lethal damage was caused to cancer cells when temperatures of 42-45°C were used for 10-60 minutes at a time. The study found that HIPEC temperatures between 42-45°C produces alterations in calcium permeability, protein denaturation, and membrane/nucleus damage within cancer cells, consequently causing cancer cell death (Cowan et al., 2017). However, due to the novelty and recent popularity of the procedure, no uniform protocol has been established regarding the temperatures at which this procedure should be administered.

There is a similar lack of standard protocol regarding the types of the chemotherapy agents used in the procedure. For example, Montori et al. (2014) states that hyperthermia positively enhances the effects of chemotherapy agents including oxaliplatin, mitomycin C, doxorubicin, cisplatin, paclitaxel, and irinotecan. However, other literature states that the use of cisplatin (a platinum-based agent) increases sensitivity of the cancer cells to the chemotherapy agent within both the platinum-resistant and platinum-sensitive cancer cell lines (Cowan et al., 2017). In general, reports show that the most common chemotherapy agents used are cisplatin, oxaliplatin, and carboplatin, with one platinum-based chemotherapy agent present during the majority of the studies reviewed in Cowan et al. (2017).

Patient selection for CRS and HIPEC is based on quantitative prognostic indicators including histopathology, imaging results, peritoneal cancer index (PCI), and the completeness of cytoreduction score (Mehta et al., 2016). The peritoneal cancer index quantitatively assesses the degree of cancer distribution throughout the pelvic and abdominal regions (Mehta et al., 2016). This process is performed by dividing the regions into 13 subsections to assess the distributions and size of tumors (Mehta et al., 2016). Additionally, the completeness of resection status (R status) plays a factor in selecting patients for HIPEC due to the status's impact on

survival. Resection statuses range from R0 to R2-C, with R0 representing no visible tumor nodules remaining after surgery (complete resection) and negative cytologic findings (Shen et al., 2003). R1 status shows no visible residual tumor nodules, but positive cytologic findings (Shen et al., 2003). R2-A is assigned when minimal residual tumor nodules less than 0.5cm are present. R2-B status occurs when larger residual tumor nodules remain; these nodules are greater than 0.5cm, but less than 2.0cm (Shen et al., 2003). Lastly, R2-C represents extensive residual tumor nodules that are greater than 2.0cm (Shen et al., 2003). Patients with R2 A, B, or C classification normally do not qualify for HIPEC (Mehta et al., 2016).

After a crucial patient selection period where physicians examine the overall benefits of receiving CRS and HIPEC, the treatments are then performed. CRS encompasses an abundance of surgical procedures, ranging from a visceral and parietal peritonectomy to complete colonic and rectal resection (Glockzin et al., 2009). As mentioned above, the goal of CRS is to remove all macroscopic elements of the malignant tumors. When a physician deems that complete resection has occurred (R0 or R1), the physician then performs hyperthermic intraperitoneal chemotherapy. To perform HIPEC, inflow and outflow catheters are placed into the abdominal cavity through surgical incision, with temperature probes for monitoring temperature of the chemotherapeutic agents (Glockzin et al., 2009).

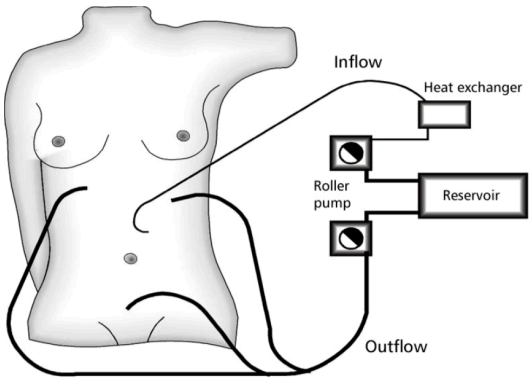

Figure 1. Diagram of HIPEC procedure (Glockzin et al., 2009).

Physicians are able to perform HIPEC using an open or closed abdominal technique (Glockzin et al., 2009). An open technique relies on the components of the abdominal cavity being open on the surgical table, while the closed technique is performed without complete surgical opening. The number one advantage to using the open technique includes increased uniformity of distribution and increased control of the circulation of the chemotherapy agents (Glockzin et al., 2009). However, risk of contamination and disease is greater when the open technique is used (Glockzin et al., 2009)

In terms of drawbacks to the procedure, patients have a risk of developing complications after receiving CRS and HIPEC. Some of these complications include bowel perforations, fistulas, abscesses, sepsis, leaks into multiple regions of the peritoneal cavity (i.e. from parts of the small intestine like the ileum, colon, etc.), and excessive bleeding (Cowan et al., 2017). Additionally, patients are extremely susceptible to bacterial infection due to the weakened immune system after treatment. For example, patients run a risk of contracting *Clostridioides difficile* (C. diff.) which causes inflammation of the colon and excessive diarrhea.

Patients receiving CRS and HIPEC normally suffer from late stage ovarian cancer or peritoneal carcinomatosis. Peritoneal carcinomatosis occurs in the peritoneum, which is an organ residing in the abdominal cavity that consists of the parietal peritoneum and visceral peritoneum (Mehta et al., 2016). The parietal peritoneum lines the abdominal wall while the visceral peritoneum covers both the pelvic and abdominal organs, leaving potential areas of space for cancer cells to metastasize between the walls of the abdominal and pelvic cavities (Mehta et al., 2016). Due to the spaces between the linings and the walls, as well as the immense number of foldings within the peritoneal cavity, primary tumors have an increased possibility of developing and spreading (Mehta et al., 2016). Sometimes these cancers spread due to disease progression, and other times due to poor prognosis or catching the cancer too late (Coccolini et al., 2013).

When cancer in the peritoneal cavity spreads, it spreads in three ways. The first includes random proximal distribution where the cancer cells spread randomly within the peritoneal cavity typically found in moderate to high-grade counters (Coccolini et al., 2013). The second includes complete redistribution where the cells close to the primary tumor do not stick to the peritoneal surface; characteristically, this occurs in tumors with low aggressiveness (Coccolini et al., 2013). The third and final way includes widespread cancer distribution where the malignant cancer cells produce mucus that hinders cell adherence and is most frequently found in the most aggressive tumors (Coccolini et al., 2013). Compared to other colorectal cancers, peritoneal carcinomatosis is the second-leading cause of death, with metastatic disease in the liver coming in second (Verwaal et al., 2003).

Ranking fifth in leading causes of death of American women, most forms of ovarian cancer metastasize to the peritoneal cavity, with an abundance of tumor cells located within the peritoneum (Cowan et al., 2017). Protocols for treatment of ovarian cancer range from systemic intravenous chemotherapy to non-systemic (localized) intraperitoneal chemotherapy. Non-heated, localized intraperitoneal chemotherapy compared to intravenous delivery of chemotherapy has been shown to increase access to tumor cells by the chemotherapy agent, as well as increase the toxicity of the chemotherapeutic agent (Cowan et al., 2017). Additionally, studies have also shown that when distributed locally and intraperitoneally, chemotherapy agents exhibit a longer half-life within the cavity (Cowan et al., 2017). This results in a decreased metabolism of the chemotherapy agent administered and hence a greater half-life. In general, many hospitals around the United States have not actively pursued using localized intraperitoneal chemotherapy due to overarching concerns regarding the potential risks of higher toxicity and the greater cost of the treatment.

Common past treatments of peritoneal carcinomatosis and late-stage ovarian cancer included regular systemic chemotherapy using various chemotherapy agents such as oxaliplatin and floxuridine (Verwaal et al., 2003). Cowan et al. (2017) states that an additional common practice for treatment of advanced ovarian cancer included primary cytoreductive surgery that was proceeded by platinum-based chemotherapy; those procedures were then followed by interval cytoreductive surgery. Interval cytoreductive surgery can be defined as cytoreductive surgery that occurs after approximately two or three cycles of systemic chemotherapy (Tangjitgamol et al., 2013). Today, intraperitoneal cancer continues to produce a high mortality rate, even in the face of current treatments like systemic chemotherapy. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy could represent the solution needed to reduce these high mortality rates, in turn increasing morbidity rates resulting from metastasized intraperitoneal carcinomatosis with implementation of this procedure as common practice.

BODY

Verwaal et al. (2003) conducted a study of CRS and HIPEC versus systemic chemotherapy and palliative surgery involving 105 randomly assigned patients. The control group of standard treatment consisted of 51 standard therapy patients who possessed peritoneal carcinomatosis of colorectal cancer, while the experimental group consisted of 49 patients with similar diagnoses (Verwaal et al., 2003). Some patients within the control (standard) group began their treatment process with bypass or stoma surgery performed due to obstructions within the intestine, but these surgeries were performed before random assignment occurred (Verwaal et al., 2003). Overall, all patients assigned to the control group received chemotherapy treatments from their personal oncologists (Verwaal et al., 2003). These treatments included 400mg/m^2 of fluorouracil and 80mg/m^2 of leucovorin injected intravenously on a weekly basis for 26 weeks (Verwaal et al., 2003).

All CRS and HIPEC procedures for the 49 patients within the experimental group were performed at the Netherlands Cancer Institute and followed the same protocol as outlined by Sugarbaker et al. (Verwaal et al., 2003). First, a laparotomy (surgical incision within the abdominal cavity) was made from the xyphoid to the pubis for the purpose of determining the size/presence of macroscopic tumor nodules in seven regions of the abdominal cavity; tumor size was tracked using four categories: none, less than 1cm, 1 to 5 cm, and more than 5cm (Verwaal et al., 2003). Cytoreductive surgery was then performed by stripping the parietal peritoneum of tumor nodules to fulfill the goal of complete elimination of residual macroscopic tumor nodules; if nodules remained within the cavity, the residual nodules must have been less than 2.5mm in overall thickness (Verwaal et al., 2003). Due to the nature of the process, some patients' internal organs were resected to ensure proper function; organs included the rectum, colon, gall bladder, stomach, and spleen (Verwaal et al., 2003). Physicians then determined the amount of residual

tumor present using a scale of R-1 (absence of residual tumor), R-2a (<2.5mm), and R-2b (>2.5mm), as well as determined the length and total blood loss during the operation (Verwaal et al., 2003).

The specific procedure used for hyperthermic intraperitoneal chemotherapy began with the skin from the laparotomy being pulled against a retractor to increase the volume of the abdominal cavity, ensuring that more chemotherapy would come into contact with the necessary areas (Verwaal et al., 2003). A central opening was made within the laparotomy to centrally place an inflow catheter and multiple outflow catheters in the pelvis below the left and right diaphragm that separates the thoracic cavity from the abdominal cavity, as well as a roller pump and heat exchanger to ensure the most optimal distribution of heat and chemotherapy agents (Verwaal et al., 2003). Mitomycin C was heated to 41°C - 42°C and then distributed at a dose of 17.5mg/m^2 then 8.85mg/m^2 every 30 minutes until a maximum of 70mg was reached (Verwaal et al., 2003). At the conclusion of the procedure, the chemotherapy was drained from the abdominal cavity using the outflow catheters (Verwaal et al., 2003).

All patients were required to be seen by a physician every 3 months for 2 years, then every 6 months following the 2-year period for a CEA (carcinoembryonic antigen) test that measures proteins in the blood released by cancer cells, as well as an abdominal CT scan (Verwaal et al., 2003). This leads into the statistical analysis portion of the study where overall survival was measured by calculating time from the beginning of the randomized placement process to death from any cause including outside factors (Verwaal et al., 2003). The results showed that of the 51 patients randomly assigned to the control group, 1 patient did not meet the qualifications to go through with the study, bringing the control sample size down to 50 (Verwaal et al., 2003). For various unforeseen reasons, the final number of patients who received the control treatment was 38 (Verwaal et al., 2003). This number is less than the 49 total patients

within the experimental group who actually underwent CRS and HIPEC (Verwaal et al., 2003). After a follow-up time of 21.6 months (median), 20 patients within the control group were still alive compared to 30 patients in the experimental group, showing that CRS followed by HIPEC increased rate of survival by a statistically significant percentage (Verwaal et al., 2003). In addition to increasing survival time, results also showed that resection status and number of regions with residual tumor was a contributing factor to survival after CRS and HIPEC. Verwaal et al. (2003) states that a fully (or mostly) complete resection during CRS should be required as a prerequisite for the procedure if physicians would like a more favorable outcome for their patients.

Shen et al. (2003) sought to explore the relationship between overall survival rate after CRS / HIPEC and four independent factors that include primary site of cancer tumors, resection status after CRS (R0 to R2c), presence versus absence of liver metastases, and nonadenocarcinoma histologic features. Overall, the procedures used for CRS and HIPEC within the study by Shen et al. (2003) mostly mirrored the protocol used by Verwaal et al. (2003) except for classification of resection. Verwaal et al. (2003) used R-1 to represent absence of residual tumor, R-2a for residual tumors less than 2.5mm, and R-2b for residual tumors greater than 2.5mm. Shen et al. (2003) used centimeters instead of millimeters to measure residual tumor size, as well as a 5-point scale for resection status (Table 1). The lack of standardized protocol for CRS and HIPEC could be the reason for such a discrepancy.

Table 1. Resection status after CRS (Shen et al., 2003).

Resection Status	Description of Status
R0	no visible tumor remaining (negative cytologic findings)
R1	no visible tumor remaining (positive cytologic findings)
R2a	minimal residual tumor nodules (≤ 0.5cm)
R2b	gross residual tumor nodules (> 0.5cm, ≤ 2cm)
R2c	extensive tumor nodules remaining (> 2cm)

The sample size of the Shen et al. (2003) study consisted of 109 total patients who received the CRS and HIPEC procedures. Each CRS and HIPEC procedure was conducted by the same physician at the Wake Forest University School of Medicine between 1991 and 1997 (Shen et al., 2003). This was done to control for variable techniques between physicians. Temperatures of the mitomycin C ranged from 39.5°C to 40.5°C during the application of HIPEC (Shen et al., 2003) in contrast to the HIPEC temperatures of 41°C to 42°C used in the study by Verwaal et al. (2003). Additionally, during the procedure, the physician massaged the abdomens of the patients to ensure that the chemotherapy agents made contact with as many peritoneal surfaces as possible (Shen et al., 2003). Shen et al. (2003) also mentioned that the total time of chemotherapy distribution during HIPEC was 120 minutes, compared to 90 minutes in the study conducted by Verwaal et al. (2003).

Follow-up occurred at 1 month and 3 months post-procedure, then every 3 months for up 12 months post-operation (Shen et al., 2003). Additionally, patients received abdominal and pelvic scans when clinically indicated, but also at the 3, 6, and 12-month marks after the procedure (Shen et al., 2003). Shen et al. (2003) mentions that some patients received systemic chemotherapy after referral to their medical oncologists but did not specify if additional systemic chemotherapy affected the outcome of the study.

The results of the study showed that there was a higher proportion of surviving patients if the primary site of the cancer was just the appendix and no other area of the body (Shen et al., 2003). No indication of liver metastasis and absence of adenocarcinoma through histologic testing were also factors observed in a higher proportion of surviving patients within the study (Shen et al., 2003). Complete resection during cytoreductive surgery (R0) was shown to be the most significant factor in predicting overall survival. Hyperthermic chemotherapy works synergistically with administration of chemotherapeutic compounds directly into the

intraperitoneal cavity (as opposed to systemic administration) and complete resection status to produce the most effective results (Shen et al., 2003). Shen et al. (2003) indicates that the efficacy of these synergistic effects depends heavily on the residual tumor ratio, indicated by an increased survival rate in patients who possessed peritoneal carcinomatosis in structures that were able to be removed (colon, spleen, gallbladder, etc.). Of the 109 patients within the study, the survival rate at 12 months post-operation was 61%, while the rate at 36 months (3 years) post-operation was 33% (Shen et al., 2003). These results were not affected by the fact that not all of the 109 patients received the full, intended HIPEC treatment: 67 patients received 2 hours of intraperitoneal perfusion with a dose of 40mg of mitomycin C, 14 patients underwent 2 hours of perfusion with only 30mg of mitomycin C, and 22 patients only received 1 hour of mitomycin C perfusion with varying concentrations of MMC given (Shen et al., 2003). Patients with a complete or nearly complete resection status (R0 and R1) had a significantly greater survival rate ($p < 0.001$, 68% survival) 36 months post-CRS/HIPEC as compared to a 21% survival rate of patients within the R2 resection category (Shen et al., 2003).

Shen et al. (2003) used exponential cellular kinetics to describe the benefits of using intraperitoneal chemotherapy and cytoreductive surgery with the diagnosis of peritoneal carcinomatosis. Since tumor cell growth is exponential in the first stages of the cell cycle, the tumor cells utilize an abundant amount of blood for exponential growth. However, the blood supply and growth of the tumor cells decreases as the tumor grows in size, resulting in an increased number of tumor cells entering the nonproliferation stage of the cell cycle where spread stops. As a result, the use of cytoreductive surgery (debulking) stimulates increased tumor cell growth in response to the removal of cancerous tumor cells, ultimately increasing the effectiveness of chemotherapy agents applied directly to the tumor cells since these cells perform constant aerobic glycolysis and replicate at an extremely increased rate (Shen et al., 2003).

Patient selection is key in the administration of cytoreductive surgery followed by hyperthermic chemotherapy. From 1-Jan-2010 to 31-Dec-2017, 28 patients with gastric adenocarcinoma underwent hyperthermic intraperitoneal chemotherapy at 7 academic hospitals in the United States (Kimbrough et al., 2019). Even though a diagnosis of gastric cancer does not necessarily indicate peritoneal carcinomatosis, the low number of 28 shows that this procedure is offered on a specific, limited basis within the United States. Of the 28 patients in the study, 96% of them had received systemic chemotherapy treatments following HIPEC (Kimbrough et al., 2019). Seventy five percent of patients experienced a minimum of 1 complication with the HIPEC procedure, indicating that the procedure can produce unforeseen consequences. From the perspective of Kimbrough et al. (2019), patient selection criteria for CRS with HIPEC remains extremely unclear and does not support the biological differences seen among patients with gastric cancer or peritoneal carcinomatosis (Kimbrough et al., 2019). They suggest that hyperthermic intraperitoneal chemotherapy should be limited to clinical trials and not used as a standard procedure for treatment of progressive cancers.

In the study conducted by Verwaal et al. (2003), patients' eligibility rested on possessing peritoneal metastases of colorectal adenocarcinoma with no signs of liver/lung metastases (obtained from CT scans of the abdomen and x-rays of the chest). The patient requirements included being younger than 71 years of age and healthy enough to undergo major surgery, as shown by regular bone marrow indices and regular functions of the liver and renal system (Verwaal et al., 2003). It is interesting to note that patients who underwent systemic chemotherapy with fluorouracil within 1 year of random assignment were not initially eligible for participation in the study. However, they were then deemed suitable due to an amendment to the patient specifications after 1 year of the study (Verwaal et al., 2003). Randomization of the patients occurred through a computer software system that split the patients into groups relating

to presentation of the cancer (primary or recurrence) and site of the cancer, specifically appendix, colon, rectum (Verwaal et al., 2003). On the other hand, Shen et al. (2003) had minimal eligibility requirements for their study. The Shen et al. (2003) study was open to any patient with peritoneal carcinomatosis from both gastrointestinal and non-gastrointestinal primary sites without any presentation of metastasis into other areas of the body besides the abdomen.

Overall, the survival rates of patients within the three studies vary (Table 2). Verwaal et al. (2003) states that 30 patients who received CRS and HIPEC (of 49) were still alive after a median follow-up time of 21.6 months, versus 20 patients (of 38) who survived from the control group of standard systemic chemotherapy. Shen et al. (2003) reports a 1-year overall survival rate of 61% and a 3-year overall survival rate of 33%. These percentages can be interpreted as about 66 patients out of 109 patients were still alive after 12 months post-treatment with CRS and HIPEC, and about 35 patients were still alive after 3 years post-treatment. However, Shen et al. (2003) states that the median overall survival time was 16 months post-treatment with CRS and HIPEC. Lastly, Kimbrough et al. (2019) states that the median survival for 23 patients who underwent CRS and HIPEC was 10 months, with an overall survival rate of 38% after 12 months post-treatment.

Table 2. Summary of Survival Data

Literature	Survival Rate (CRS and HIPEC)	Survival Rate (systemic chemotherapy)	Median Survival (CRS and HIPEC)	Median Survival (systemic chemotherapy)
Verwaal et al. (2003)	*21.6-month follow-up* 61.2%	*21.6-month follow-up* 52.6%	22.4 months	12.6 months
Shen et al. (2003)	*12-month follow-up* 61% *36-month follow-up 33%*	N/A	16 months	N/A
Kimbrough et al. (2019)	*12-month follow-up* 38%	N/A	10 months	N/A

CONCLUSION

Studies have shown that cytoreductive surgery paired with hyperthermic intraperitoneal chemotherapy can be an effective option for patients with types of cancer including peritoneal carcinomatosis (Verwaal et al., 2003), late stage ovarian cancer (Cowan et al., 2017), and gastric adenocarcinoma (Kimbrough et al., 2019). The study by Verwaal et al. (2003) shows that the group who received CRS combined with HIPEC possessed a higher survival rate and median survival time in months compared to the group who received regular systemic chemotherapy. Since the two other studies did not compare results to patients who received regular systemic chemotherapy, a definitive conclusion cannot be made about the best treatment for patients with peritoneal carcinomatosis, late stage ovarian cancer, and gastric adenocarcinoma.

However, since the treatment option is relatively new and not common practice, protocols differ from physician to physician. The lack of optimal temperature for the HIPEC procedure represents one way that protocols differ. For example, temperatures of mitomycin C ranged from 39.5°C to 40.5°C during the application of HIPEC within Shen et al., (2003), while Verwaal et al. (2003) utilized temperatures of 41°C to 42°C. Although, this difference in range is not as drastic as used in initial studies where temperatures of applied chemotherapy agents ranged from 42°C to 45°C (Cowan et al., 2017).

Each study had its own shortcomings, reflecting the lack of standardized protocol for CRS and HIPEC. Verwaal et al. (2003) used different chemotherapy agents between the experimental and control groups. This could mean that the survival rates reported within the study might not be comparable between the experimental group (CRS and HIPEC) and control group (systemic chemotherapy). When compared to the study by Shen et al. (2003), Verwaal et al. (2003) used millimeters to measure resection status while Shen et al. (2003) uses centimeters. Millimeters are a much more accurate form of measurement compared to centimeters. This

indicates that the results from Shen et al. (2003) may not be comparable to the results from the experimental group within Verwaal et al. (2003). Additionally, Verwaal et al. (2003) states that a mortality rate of 8% within the study could be attributed to complications from the cytoreductive surgery and not the hyperthermic intraperitoneal chemotherapy itself.

Verwaal et al. (2003) also discusses the importance of patient selection when considering CRS and HIPEC. Patients who had cancer nodules in 6 or 7 regions of the abdominal cavity fell into 80% of the treatment-related deaths, showing that increased tumor presence relates to decreased survival (Verwaal et al., 2003). Shen et al. (2003) discusses similar ideas, stating that patient selection is pivotal in controlling for preventable premature deaths in patients; all patients with peritoneal carcinomatosis should not receive CRS and HIPEC. On the other hand, the study by Kimbrough et al. (2019) did not show positive results when comparing many different studies of CRS and HIPEC, yet the authors agree that patient selection plays a key role in the success of CRS and HIPEC. Kimbrough et al. (2019) indicates that CRS and HIPEC should only be limited to clinical trials using patients with low tumor load.

Through this research, it has become clear that cytoreductive surgery paired with hyperthermic chemotherapy should be utilized as a “last resort” procedure under intense patient selection processes due to the complications that can follow from the treatment. Although each primary article did not delve into patient complications in an in-depth manner, the increased survival rates can outweigh the potential complications if the patient begins in critical condition. Cytoreductive surgery paired with hyperthermic chemotherapy seems to be a procedure that capitalizes on human ethics. Do the risks outweigh the benefits (i.e. would patients be living with more morbidity) if they were to receive CRS paired with HIPEC? To expand upon these studies, I would utilize as much time as possible to choose patients with similar peritoneal carcinomatosis diagnoses (i.e. origin of tumor, overall health) to compare CRS and HIPEC with intravenous

systemic chemotherapy. This would require years of study but could benefit humankind in the future.

ACKNOWLEDGMENTS

Thank you to Dr. Connaughton for the extensive advice and comments throughout the entire SCE process! Thank you to all of the faculty within WAC's Department of Biology for pushing me to do my best in each aspect of my academic career!

LITERATURE CITED

Coccolini, F., Gheza, F., Lotti, M., Virzì, S., Iusco, D., Ghermandi, C., … Catena, F. (2013). Peritoneal carcinomatosis. *World journal of gastroenterology*, *19*(41): 6979–6994. doi:10.3748/wjg.v19.i41.6979.

Cowan, R. A., O'Cearbhaill, R.E., Zivanovic O., Chi D. S. (2017). Current status and future prospects of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) clinical trials in ovarian cancer. *International Journal of Hyperthermia, 33*(5): 548-553. doi: 10.1080/02656736.2017.1283066.

Glockzin, G., Schlitt, H. J., Piso, P. (2009) Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World Journal of Surgical Oncology, 7*(5). doi:10.1186/1477-7819-7-5.

Kimbrough, C. W., Beal, E., Abdel-Misih, S., Pawlik, T. M., Cloyd, J. M. (2019). Survival outcomes among patients with gastric adenocarcinoma who received hyperthermic intraperitoneal chemotherapy with cytoreductive surgery. *JAMA Surgery,* 154(8): 780-782. doi:10.1001/jamasurg.2019.1698.

Mehta, S. S., Bhatt, A., Glehen, O. (2016). Cytoreductive surgery and peritonectomy procedures. *Indian J Surg Oncol*, *7*(2): 139-151.

Montori, G., Coccolini, F., Ceresoli, M., Catena, F., Colaianni, N., Poletti, E., Ansaloni, L. (2014). The treatment of peritoneal carcinomatosis in advanced gastric cancer: state of the art. *International Journal of Surgical Oncology 2014*(912418). doi: s http://dx.doi.org/10.1155/2014/912418

Neuwirth, M. G., Alexander, H. R., Karakousis, G. C. (2015). Then and now: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), a historical perspective. *Journal of Gastrointestinal Oncology*, *7*(1), 18-28. doi: 10.3978/ j.issn.2078-6891.2015.106.

Shen, P., Levine, E. A., Hall, J., Case, D., Russell, G., Fleming, R., McQuellon, R., Geisinger, K. R., Loggie, B. W. (2003). Factors predicting survival after intraperitoneal hyperthermic chemotherapy with mitomycin C after cytoreductive surgery for patients with peritoneal carcinomatosis. *Arch Surg 138*: 26-33.

Smith, M. E & Nathan, H. (2019). Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: safety is only half of the story. *JAMA Network Open*, *1*(2). doi: 10.1001/jamanetworkopen.2018.6839.

Tangjitgamol, S., Manusirivithaya, S., Laopaiboon, M., Lumbiganon, P., Bryant, A. (2013). Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev*, 4: CD006014. doi:10.1002/14651858.CD006014.pub6.

Verwaal, V. J., van Ruth, S., de Bree, E., van Slooten, G., van Tinteren, H., Boot, H., Zoetmulder, F. A. N. (2003). Randomized trial of cytoreduction and hyperthermic

intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *Journal of Clinical Oncology 21*(20): 3737-3743. doi: 10.1200/JCO.2003.04.187.