Outcome and Safety of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) +/- Intraoperative Radiation Therapy (IORT) in the Management of Peritoneal Sarcomatosis: A Real-World Experience

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Abstract

\textbf{Background:} Peritoneal sarcomatosis (PS) is an aggressive disease; cytoreductive surgery (CRS) could be curative.

\textbf{Aim:} Can the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) +/- intraoperative radiation therapy (IORT) overcome treatment failure with an overall survival benefit.

\textbf{Methods:} Retrospective review of the medical records of patients with PS treated by CRS, HIPEC and IORT at a comprehensive cancer center in the period between 2011-2016.

\textbf{Results:} Twenty-four patients were identified. Fifteen were men and their median age was 58 years. Liposarcoma was the most frequent diagnosis (50%). Cytoreduction completeness (CC) score 0/1 was achieved in 19 patients, with a median pathological peritoneal cancer index (pPCI) of 12. Intraoperative radiation therapy was given in 16 patients. Eight patients developed grade III-IV Clavien-Dindo post-operative complications and 1 patient died 5 days post-operative. Adjuvant chemotherapy was received in 9 patients. After a median follow-up of 28.5 months, the median PFS was 20.7 months, while the estimated 2- and 4-year PFS were 37.1% and 19.1%, respectively. The median OS was 176.5 months and the estimated 2- and 4-year OS were 95.8% and 79.8%, respectively. In the univariate analysis, the PFS differed significantly according to the CC score only. The median PFS for patients with CC 0-1 was 23.8 vs. 8.8 months for those with CC 2-3 (p = 0.027).

\textbf{Conclusions:} The addition of HIPEC and IORT to CRS in the management of PS is feasible and safe. Comparing our results to several studies, this multimodality approach seems to improve local and regional control rates. A larger cohort of patients is needed for further evaluation and to give a concrete conclusion.

\textbf{Keywords:} Peritoneal sarcomatosis, Cytoreductive Surgery, Hyperthermic intraperitoneal chemotherapy, Intraoperative radiation therapy
Introduction

Soft tissue sarcomas represent about 1% of all adult malignancies, a third of them originate from the abdominal viscera or retroperitoneum. They are characterized by the high ability for hematogenous spread, typically to the lungs, liver, and direct spread to involve other peritoneal surfaces and adjacent organs. They had also; a high post-surgical locoregional failure rate ranging from 35 to 82%.

Peritoneal sarcomatosis (PS) presents a diffuse form of intra-abdominal dissemination; either due to recurrence or spread by seeding to the nearby peritoneal surface. It could be the initial diagnosis, but more frequently occurs at recurrence, most probably as a result of tumor spillage during the initial resection. The prognosis of patients with PS is poor, therefore the ultimate need for research to find the best treatment options increased.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has achieved prolonged survival in patients with peritoneal surface disease from a variety of epithelial tumors of appendicular, colorectal, and mesothelioma origins.

There is great controversy about the use of CRS-HIPEC in PS patients, probably due to the high ability of sarcoma for hematogenous spread and the lack of effective chemotherapeutic agents.

Intraoperative radiation therapy (IORT) is a highly conformal radiation therapy modality that is administered in the operating theater. It has been used in a variety of malignancies, including retroperitoneal sarcoma, in order to increase the tumor radiation dose without exceeding normal tissue tolerance doses for better tumor local control.

Many studies have addressed the prognostic value of many factors such as: KI-67 index, pretreatment inflammatory markers such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in soft tissue sarcoma patients reporting that patients with high levels of these markers have poor prognosis and survival.

In this study, we reviewed the outcome of PS patients who had been treated with CRS-HIPEC +/- IORT, including postoperative morbidity and mortality, local control rate, progression-free survival (PFS), overall survival (OS) and the significant correlation of multiple variables including the KI-67 index, NLR and PLR with survival.

Methods

The medical records of 24 PS patients treated with the multimodal approach including (CRS and HIPEC +/- IORT) at the King Faisal Specialized Hospital and Research Center, Riyadh, Saudi Arabia, in the period between January 2011 and December 2016 were retrospectively reviewed. The data collected included age, sex, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, histopathological subtype, histological grade, ki-67 index (number of KI-67 positive tumor cells), initial NLR, initial PLR, American Joint Committee on Cancer (AJCC) stage, preoperative tumor size, preoperative treatment received (chemotherapy or radiation therapy), operational details (including completeness of cytoreduction (CC), pathological peritoneal cancer index (pPCI) and chemotherapeutic agent used in HIPEC), the dose of IORT, postoperative complications according to the Clavien-Dindo classification system, postoperative treatment received, pattern of disease recurrence (locoregional, distant or combined) and current status of patient (alive with a disease or alive without disease or dead).

The HIPEC technique is used in our center in addition to CRS in the management of PS patients with the following inclusion criteria: (1) ECOG performance status ≤2, (2) satisfactory laboratory work, (3) proven diagnosis of PS confirmed by preoperative biopsy, (4) no evidence of distant extra abdominopelvic metastases to the liver, lungs, brain or bones. The details of the operative and HIPEC technique were published earlier in our previous studies.

After completion of the surgical procedure, residual tumor assessment was performed intraoperatively using the standard CC scores, as documented by Sugarbaker, CC-0 (no gross residual disease) was regarded as complete cytoreduction, whereas CC-1 (up to 2.5 mm gross residual disease)
was regarded as near-complete cytoreduction. Intraoperative radiation therapy is usually used in our center for patients with PS using Mobetron® in a dose range of 10-20 Gy. The total dose of IORT received depended on the extent of the residual tumor after resection. IORT was used in patients with CC-0 and CC-1 only. In patients with CC-0, a dose of 10-12 Gy is used. For the patients CC-1(with residual tumors less than 1mm), a dose of 12-15 Gy is used. For those with CC-1(residual tumor 1-2.5 mm), a dose of 15 to 20 Gy. A dose between 10 and 20 Gy was considered a safe dose with minimal postoperative side effects, taking in consideration other factors as the location of nearby risk structures and the dose of previous radiation therapy if present.

Many therapeutic agents for HIPEC were used as a combination of cisplatin (50 mg/m²) plus doxorubicin (15 mg/m²) infused over 90 minutes or single agent melphalan (60 mg/m²) infused over 60 minutes. The choice of HIPEC therapeutic agent depends on the case as agreed by the multidisciplinary medical oncology and surgical oncology team treating.

During the HIPEC procedure, all hemodynamic and cardiopulmonary parameters were strictly monitored. After completion of the entire procedure, including CRS, HIPEC +/- IORT, all patients were transferred to the intensive care unit (ICU) for 1 to 3 days (median:1 day) and then transferred to the surgical ward for recovery.

Postoperative complications were evaluated according to the Clavien-Dindo grading system (Table 1).

In some cases, adjuvant treatment (chemotherapy, radiation therapy, or both) was planned if deemed indicated based on the postoperative pathological and radiological data.

All patients were kept at regular follow-up, every 3 months during the first 2 years after HIPEC, every 6 months for another 2 years, then annually. Follow-up investigations included complete blood work, chest, abdomen, and pelvis CT, abdominal magnetic resonance imaging + / - PET-CT (when indicated).

### Table 1: The Clavien-Dindo grading system of postoperative complications

| Grade  | Definition |
|--------|------------|
| Grade 1 | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside. |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. |
| Grade III-a | Intervention not under general anesthesia. |
| Grade III-b | Intervention under general anesthesia. |
| Grade IV | Life-threatening complications (including CNS complications) requiring IC/ICU-management. |
| Grade IV-a | Single organ dysfunction (including dialysis). |
| Grade IV-b | Multi-organ dysfunction. |
| Grade V | Death of the patient. |

## Results

Fifteen males and nine females were reviewed, the median age at the time of CRS was 58 (31-77) years. Seventeen (71%) patients had stage III disease according to AJCC staging system. Ki-67 were detected in 14 (58%) patients with a variable range of 6-370/10 high power field (HPF), with a median value of 56/10 HPF. Different neoadjuvant chemotherapy protocols were used in 5 (20.8%) patients; (imatinib, doxorubicin and combined
ifosfamide-etoposide). Three patients received neoadjuvant radiation therapy with a dose of 45Gy/25 fractions using intensity modulated radiation therapy technique. Detailed patients and treatment characteristics are listed in Table 2.

### Table 2: Baseline characteristics of 24 patients with peritoneal sarcomatosis and their pre-surgical treatment

| Characteristic                                | Description          |
|-----------------------------------------------|----------------------|
| **Age in years at CRS time** (median [range]) | 58 (31-77)           |
| **Gender**                                   |                      |
| Male                                          | 15 (62.5%)           |
| Female                                       | 9 (37.5%)            |
| **ECOG performance status**                  |                      |
| 1                                             | 14 (58%)             |
| 2                                             | 10 (42%)             |
| **Histopathological subtypes**                |                      |
| Liposarcoma                                   | 12 (50%)             |
| Leiomyosarcoma                                | 4 (16.7%)            |
| Gastrointestinal stromal tumor                | 3 (12.5%)            |
| Others                                        | 5 (20.8%)            |
| **Histopathological grades**                  |                      |
| G1                                            | 7 (29%)              |
| G2                                            | 9 (37.5%)            |
| G3                                            | 8 (33.5%)            |
| **KI-67 positive tumor cells (KI-67 index)**  | 14 (58%)             |
| **KI-67 index** (median [range])              | 56 (6-370/10 HPF)    |
| **Pre-operative tumor size in cm** (median [range]) | 12 (6-21)          |
| **AJCC Stage**                                |                      |
| I                                             | 7 (29%)              |
| IIIa                                          | 6 (23%)              |
| IIIb                                          | 11 (46%)             |
| **Neoadjuvant chemotherapy**                  |                      |
| Given                                         | 5 (20.8%)            |
| Not given                                     | 19 (79.2%)           |
| **Neoadjuvant radiation therapy**             |                      |
| Given                                         | 3 (12.5%)            |
| Not given                                     | 21 (87.5%)           |

**ECOG**: Eastern Cooperative Oncology Group; **AJCC**: American Joint Committee on Cancer

All patients underwent CRS and HIPEC to achieve cure. The CC score (0/1) was achieved in 19 (79.17%) patients with a median pPCI of 12 (range: 3 to 28). Melphalan was the most used chemotherapeutic agent in HIPEC, it was used in 16 (66.67%) patients. IORT was given in 16 (66.67%) patients (dose range 10-15 Gy), Table 3.

Different adjuvant chemotherapy protocols were used in 9 (37.5%) patients including (imatinib, doxorubicin, and ifosfamide, single agent doxorubicin and single agent gemcitabine).

Grade I CD complications occurred in 6 (25%) patients and grade II in 9 (37.5%). Nine (37.5%) patients developed ≥ grade III Clavien-Dindo (CD) complications, and 1 (4.2%) patient died (grade V CD) 5 days after operation in the ICU due to massive pulmonary embolism despite full coverage of prophylactic anticoagulants. The details of grade III and IV CD complications are illustrated in Table 4.

After a median follow up of 28.5 (2-70) months, the median overall (locoregional and systemic) PFS was 20.7 months, while the estimated 2 and 4 years overall PFS were 37.1% and 19.1%, respectively (Figure 1).

Fifteen (62.5%) patients developed systemic progression (two of them developed both locoregional and systemic progression). The lung was the site most affected at the time of progression in 8/15 (53.3%) patients. Isolated locoregional progression occurred in two (8.3%) patients. The 2 cases with isolated local progression underwent redo CRS and HIPEC with an average of 36 months between the first and redo surgery. The estimated 2- and 4-year locoregional PFS were 88.4% and 60.6%, respectively, while the estimated 2 and 4 years systemic PFS were 37.1% and 27.8%, respectively.
The median OS was 176.5 months, with estimated 2- and 4-year OS were 95.8% and 79.8% respectively (Figure 2).

For PFS, in the univariate analysis, the CC score was significantly correlated with PFS as the median PFS for patients with CC 0-1 was 23.8 months vs 8.8 months for those with CC 2-3 (p = 0.027). Progression-free survival did not differ significantly according to the other variables studied (Table 5). Similarly, none of the studied variables was associated with a significant difference in OS in the univariate analysis.

Table 4: Management and outcome of grade III and IV Clavein Dindo (CD) complications

| CD Grade | n (%) | Complication          | Management                                | Outcome   |
|----------|-------|------------------------|-------------------------------------------|-----------|
| III a    | 2 (8.3) | Pleural effusion       | Pleurocentesis                            | Recovered |
|          | 1 (4.2) | Pancreatic fistula     | Ultrasound-guided drainage                | Recovered |
|          | 1 (4.2) | Urinary bladder fistula| Cystoscopy and Foley's catheter insertion | Recovered |
| III b    | 1 (4.2) | Bowel leakage          | Exploration                               | Recovered |
|          | 1 (4.2) | Bleeding               | Exploration and hematoma evacuation       | Recovered |
|          | 1 (4.2) | Wound dehiscence       | Debridement and flap                      | Recovered |
| IV a     | 1 (4.2) | Respiratory failure    | Resuscitation in the intensive care unit  | Recovered |

Table 5: univariate analysis correlation of multiple parameters with progression-free and overall survival

| Survival | Parameter                                | Estimated median survival (months) | p value |
|----------|------------------------------------------|-------------------------------------|---------|
| Progression-free survival | Cytoreduction completeness (CC) score | 0, 1 23.8 | 0.027 |
|          | Pathological peritoneal cancer index (pPCI) | 2.3 8.8 | 0.382 |
|          | ≤ 10 23.9 | | |
|          | 10-20 20.2 | | |
|          | > 20 8.4 | | |
|          | Histopathological grade | G1 22.6 | 0.316 |
|          | G2 19.4 | | |
|          | G3 8.5 | | |
|          | Tumor size (cm) | ≤ 11 21.9 | 0.0624 |
|          | > 11 14.4 | | |
| Overall survival | KI-67 index (/10 HPF) | ≤ 50 181.8 | 0.324 |
|          | > 50 155 | | |
|          | Neutrophil-lymphocyte ratio (NLR) | ≤ 2.5 176 | 0.805 |
|          | > 2.5 104 | | |
|          | Platelet-lymphocyte ratio (PLR) | ≤ 135 180 | 0.423 |
|          | > 135 124 | | |
| American Joint Committee on Cancer (AJCC) stage | | I 184 | 0.235 |
|          | III a 160 | | |
|          | III b 87 | | |

Figure 1: Kaplan-Meier curve of progression-free survival

Figure 2: Kaplan-Meier curve of overall survival
**Discussion**

The theoretical advantage of using HIPEC after major CRS in patients with PS may come from the ability to achieve high regional concentrations of chemotherapeutic agents while keeping systemic drug levels low. This is mostly due to the slow movement of drugs from the peritoneal cavity into the plasma (peritoneal clearance) as an effect of the peritoneal-plasma barrier. The other advantage is the beneficial exposure of potential hepatic micrometastases to chemotherapeutic agents as the blood drainage of the peritoneal surface reaches the liver via the portal vein.

The benefit of using HIPEC with CRS has been thoroughly studied in many patients with peritoneal surface involvement from many cancers of epithelial origin resulting in improvement of the locoregional control, however, these benefits of using HIPEC in addition to CRS in PS have not been documented in many studies. In the current study, we have better median OS (176.5 months) in comparison to those patients in a study performed by Rossi et al., where the median OS was 34 months, Baratti et al. with reported median OS of 26.2 months and in Lim et al. study, where the median OS was 16.9 months. In the current study we have a better median PFS and OS (20.7 and 176.5 months, respectively) compared to patients enrolled in the study of Karamveri et al., where the median PFS and OS were 9 and 55 months, respectively. That survival improvement may come from the improved locoregional control (will be discussed in a separate section below) in our study compared to these studies. Despite improved survival in our study compared to other studies, strong recommendations cannot be concluded due to the great difference in histopathology, pPCI, and degree of cytoreduction between these studies.

The debate of using HIPEC in addition to CRS in PS could be related to the high ability of sarcomas for hematogenous spread as, in one series, 11% of PS patients had distant dissemination at presentation increased to 28% during the treatment course. Another series reported that distant metastasis could involve multiple organs, most commonly lung in 16% of cases followed by liver in 11% of cases. This was also evident in our study where 15 (62.5%) patients developed systemic recurrence and two (8.3%) patients developed only isolated local recurrence.

In trials to reduce the incidence of distant metastasis post-CRS and HIPEC, many investigators have used a bidirectional intraoperative intravenous chemotherapy in combination with HIPEC in patients with peritoneal metastasis from a variety of neoplasms including gastric and colorectal malignancies with promising results, however, no published data about its efficacy in PS. A recently published study conducted at our center by Hakeem et al. was assessing the safety and reported side effects of bidirectional intraoperative intravenous chemotherapy using ifosphamide in combination with HIPEC in 18 patients with peritoneal metastasis from different primaries (50% of the patients had PS). They concluded that bidirectional intraoperative intravenous chemotherapy in combination with HIPEC was generally tolerable with low rates of mild leukopenia and frequent mild thrombocytopenia, but severe suppression of platelets was uncommon. They reported nephrotoxicity in one-third of the patients. Survival data for the patients included in this study are still pending.

When comparing the locoregional recurrence rate in our study (16.6%) with other studies, Karamveri et al. showed locoregional recurrences in 65.5% of patients, Lim et al. study, the locoregional recurrence rates were 79% in patients treated with cisplatin and 68% in the group of patients treated with combination cisplatin/mitoxantrone in HIPEC regimens. In Baratti et al. study, the isolated local recurrence rate was 57.1% and in Rossi et al. study, the local recurrence rate was 67%. The improved locoregional control rate in our study in comparison to the above-mentioned studies came despite that our patients had advanced disease. This is evidenced in our study by the mean pPCI of 13.6 and pPCI-10 in 14 (58.3%) patients in comparison to patients enrolled in Karamveri et al. study where 31% had PCI-6 and in Rossi et al. study where the mean PCI was 7. The improved local regional control rate in our study could be explained by using IORT (used in 16 patients), the different agents used in HIPEC (melphalan was used in most of our patients (66.6%), in addition to highly experienced surgeons with highly efficient skills.

In the univariate analysis, the CC score was significantly correlated with PFS ($p = 0.027$). Patients with pPCI>10 had a lower median PFS compared to those with pPCI <10 although it was statistically nonsignificant. These results were compatible with other studies conducted by Rossi et al., Reese et al. and Naffouje et al.; where both CC and PCI are directly correlated with survival.
The extent of PS was evaluated intraoperatively using the peritoneal cancer index (PCI) score. Because surgical PCI (sPCI) is calculated based on a subjective evaluation of the extent of peritoneal disease during surgery, which often results in an overestimation of the score, we started to use pathological PCI (pPCI), which may be a more accurate and objective method for determining PCI and evaluating the extent of peritoneal disease. This may have a more prognostic significance.

In our study, many other factors (including Ki-67 index, tumor size, histopathological grade and stage) were associated with better either PFS or OS although none of them had statistically significant correlation with PFS or OS in spite of being significantly correlated with PFS and OS in many other studies. For example, in our study, patients with high initial level of NLR and PLR have a lower median OS compared to those patients with lower levels. However, the relation was statistically nonsignificant. These findings are comparable to results from other studies. Karamveri et al. where the histological subtype was significantly correlated with survival, as retroperitoneal liposarcoma had the best OS (median 34 months) but with 100% peritoneal relapse. This difference could be attributed to the small number of patients enrolled in our study or to a different cohort of patients.

Postoperative morbidity and mortality in our study were assessed using the Clavien-Dindo grading system. The 30 days mortality rate was 4.1%, with 8 (33.3%) patients developed grade III-IV complications (only 3 patients developed grade IIIb complications requiring intervention under general anesthesia). Karamveri et al. reported a postoperative mortality and morbidity rate of 0% and 20.7% respectively, and grade III, IV complications occurred in 13.8% of patients. In Baratti et al. study, the operative mortality and morbidity were 3.7% and 21.6% respectively, while in Rossi et al. study, the morbidity rate was 33% and the moderate to severe locoregional toxicity rate was 15%.

Multiple studies have addressed the value of using IORT in retroperitoneal sarcoma because it is difficult to completely remove with negative margin (due to its usual large size and proximity to critical structures) in addition to challenging delivery of an adequate dose of external beam radiation therapy (EBRT) postoperatively. A randomized trial conducted by Sineldar et al. reported a better local control rate with IORT in addition to low-dose postoperative EBRT compared to high-dose postoperative EBRT alone in patients with retroperitoneal sarcoma (60% vs. 20%, p < 0.05) after a median follow-up of 8 years.

Although some previous studies had addressed the benefits of combining both HIPEC and IORT with CRS in many cancer types with proved peritoneal involvement with documented improvement in locoregional control, yet to our mind this is the first study constructed initially to assess the benefit of combining both HIPEC and IORT with CRS in locoregional control of PS. In our study, we used IORT in addition to HIPEC in 66.6% of the patients taking into account the factors mentioned above that make complete surgical excision with a negative margin difficult, resulting in local control impairment. The sites, doses, and parameters of applied IORT were chosen based on the clinical judgment and discussion between the treating surgeon and radiation oncologist according to the actual findings in the operative room.

The limitations in our study include the wide variation in histopathological subtypes, treatment protocol used (neoadjuvant/ adjuvant chemotherapy, neoadjuvant radiation therapy, in addition to the different chemotherapeutic agents used in HIPEC), this diversity might be due to the rarity of such disease with few patient numbers.

Conclusions
Addition of HIPEC and IORT to CRS in the management of PS is feasible and safe. Comparing our results with several recent studies, this multimodal approach appears to improve local and regional control rates. A larger cohort of patients is needed for further evaluation and to give a concrete conclusion.

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Authors’ contribution
Conception or design: AE; Acquisition, analysis or interpretation of data: AE, AB, MAE, AA, RA, AbE; Drafting or revising the manuscript: AE, AA, RN, TA; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest
The authors declare that they have no conflict of interest to disclose.

Data availability
Deidentified individual participant data used to produce the results of this study are available from the corresponding author (AE) on request.

Ethical considerations
This research has been approved by the Research Advisory Council (RAC) of the King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia (RAC Project #2181187).

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Study registration
None.

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