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# The Use of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Pediatric Peritoneal Metastasis

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## ABSTRACT

**Mini Abstract**

The management of pediatric peritoneal metastasis and the possible role of logo regional treatment using cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). A retrospective review of the last two decades from the same peritoneal surface malignancy center.

**Objective:** Pediatric peritoneal metastasis.

**Background:** Peritoneal malignancies in children are rare, but associated with poor outcome. The CRS and HIPEC have been applied to pediatric population in recent years. The role of this treatment remains controversial due to the rarity of the disease and the limited of the cases.

**Method:** A retrospective analysis from 2003 to 2023 identified 16 children with PM who underwent CRS and HIPEC from our group.

**Results:** The median age of the children was 14 year (range 8-16,4). The histological types included Desmoid tumors (5), Wilms tumors (5), rhabdomyosarcoma (2) and other (4). The median peritoneal cancer index was 10.2 (range 6-28). There is 1 postoperative death.

The median PCI 10.2 (range 6-28). The median operation time was 6h (range 4-10). There is one postoperative death 1/16 (6.25%) due to massive pulmonary embolism in a colon cancer patient.

All patients routinely received a Levine tube (gastric tube) following CRS and HIPEC, which was removed between the 4th and 8th postoperative day. No evidence of renal failure or other metabolic complications.

The major complications according to the Clavien-Dindo were 3/16 (18.8%).

Postoperatively patients received chemotherapy (n=13) and radiotherapy (n=8) according to the different received molecular-

targeted therapy. From the 14 patients 8 relapsed after CRS + HIPEC, tree of them in peritoneal cavity and five in Liver/or Lungs. The mean time of relapse disease is 2 years after CRS plus HIPEC.

**Conclusion:** CRS+HIPEC are safe and feasible in children with good selection of the cases.

**Keywords:** Cytoreductive surgery; Pediatric peritoneal metastasis; Malignancy

## 1. Introduction

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is used to target microscopic peritoneal disease which can remain after visible disease has been surgically removed, in patients with peritoneal metastasis from different tumors which spread in the peritoneal cavity.

Research in the pediatric population is limited due to the small patient numbers and lack of clinical experience[1-3]. Additionally, inclusion criteria for pediatric cases were stringent and carefully defined. For young patients with aggressive, peritoneal-disseminated tumors, HIPEC (Hyperthermic Intraperitoneal Chemotherapy) combined with multimodal therapy may represent a promising treatment strategy[4,5].

In this study, we present our 20 years experience with different HIPEC types in pediatric patients, including reported survival outcomes, treatment-related toxicities and complications.

## 2. Patients and Methods

We presented a retrospectively analysis of pediatric peritoneal metastasis from soft tissue sarcomas, including Desmoplastic Small Round Cell Tumors (DSRCT), Rhabdomyosarcomas (RMS), Wilms tumors, also colorectal carcinomas and ovarian tumors.

During a 20 years period 2003-2023 16 cases are presented and treatment from the same surgeon (JS) in 4 different hospitals.

### 2.1. Inclusion Criteria

- **Age:** ≤18 years at time of treatment
- **Performance status:** Good functional status (e.g., ECOG ≤1 or Lansky/Karnofsky score ≥80%).
- **Organ function:** Normal renal function and normal liver function (as defined by standard laboratory thresholds).
- **Disease extent:** Locally advanced or metastatic disease confined to the abdominal cavity.
- **Treatment response:** Documented response to prior chemotherapy.
- Ethical and scientific approval from the institutional tumor and ethics boards

The HIPEC regimens were as follow:

- Doxorubicin + Cisplatin
- Cisplatin

The administered doses were Doxorubicin 15 mg/m$^2$ and Cisplatin 50 mg/m$^2$. There are 4 HIPEC cannulas placed below the diaphragm and in the pelvic cavity and the procedure performed with closed abdomen for 60 min in 42.5$^0$C Table 1.

### 2.2. Statistical analysis

Time-to-event outcomes were estimated using Kaplan-Meier curves. The log-rank test was used to assess the effect of the predictors, respectively, on Disease-Free Survival (DFS) and Overall Survival (OS). OS defined as the time from the surgery time to death (for any reason). Disease-Free Survival (DFS) was defined as the interval from the date of surgery to the first occurrence of disease recurrence or death from any cause.

Continuous variables are presented as median values and categorical variables as counts. All p values < 0.05 were considered to be statically significant. All analyses were conducted using SPSS version 26.0.3.0 (released 2019; IBM Corp.).

**Table 1**: Presents the demographic date and location of its tumor.

| No | Gender | Age | Histology | PCI | CC$_s$ | Hipec drug | Compl. |
|---|---|---|---|---|---|---|---|
| 1 | F | 12 | Other | 12 | 0 | DDP | 0 |
| 2 | F | 16 | Other | 16 | 1 | DDP | 2 |
| 3 | M | 8 | DSRCT | 6 | 0 | DOX+DDP | 0 |
| 4 | M | 14 | Other | 10 | 0 | DDP/mitomicin | 1 |
| 5 | F | 14 | RMS | 8 | 1 | DOX | 1 |
| 6 | M | 16 | DSRCT | 10 | 1 | DOX+DDP | 0 |
| 7 | M | 16 | RMS | 8 | 0 | DOX | 0 |
| 8 | F | 14 | DSRCT | 13 | 1 | DOX+DDP | 0 |
| 9 | M | 12 | Wilms | 8 | 0 | DOX | 0 |
| 10 | M | 10 | Wilms | 14 | 2 | DOX | 0 |
| 11 | M | 16 | DSRCT | 6 | 0 | DOX+DDP | 0 |
| 12 | F | 14 | DSRCT | 10 | 1 | DOX+DDP | 0 |
| 13 | F | 10 | Wilms | 10 | 0 | DOX | 0 |
| 14 | F | 15 | Wilms | 8 | 0 | DOX | 0 |
| 15 | M | 2 | Wilms | 7 | 0 | DOX | 0 |
| 16 | F | 14 | Other | 28 | 3 | Mitomicin postoperative death | 4 |

Characteristics of patients, treatment and short-term outcomes

**Abbreviate:** PCI=Peritoneal Cancer Index; CCs=Completeness of Cytoreduction Score; Complication: Clavien-Dindo Classification; DOX=Doxorubicin; DOP=Cisplatin; Other = 2 ovarian, 1 mesothelioma, 1 colon

## 3. Results

Children had a median age of 14 years (range 8-16,4). The histological types included Desmoid tumors (5), Wilms tumors (5), rhabdomyosarcoma (2) and other (4). The median peritoneal cancer index was 10.2 (range 6-28). There is 1 postoperative death.

The median PCI 10.2 (range 6-28). Procedures required a median operating time of 6h (range 4-10). There is one postoperative death 1/16 (6.25%) due to massive pulmonary embolism in a colon cancer patient.

All patients received routine gastric decompression *via* Levine tube placement following CRS/HIPEC, with removal

occurring between postoperative days 4-8. No evidence of renal failure or other metabolic complications.

The major complications according to the Clavien-Dindo were 3/16 (18.8%).

Postoperatively patients received chemotherapy (n=13) and radiotherapy (n=8) according to the different received molecular-targeted therapy. From the 14 patients 8 relapsed after CRS + HIPEC, tree of them in peritoneal cavity and five in Liver/or Lungs. The mean time of relapse disease is 2 years after CRS plus HIPEC.

### 3.1. Pediatric Malignancies

Of the 16 patients (8 girls, 8 boys) considered in the analysis the median age at surgery was 14 years, ranging from 8 to 16 years. 8 patients (50%) have died whereas 8 (50%) were the censored cases. The median overall survival time was 67 months (95% CI: 13.1 – 120.9). The median disease-free survival time was 46 months (95% CI: 0 – 110) (Figure 1 and Table 2)

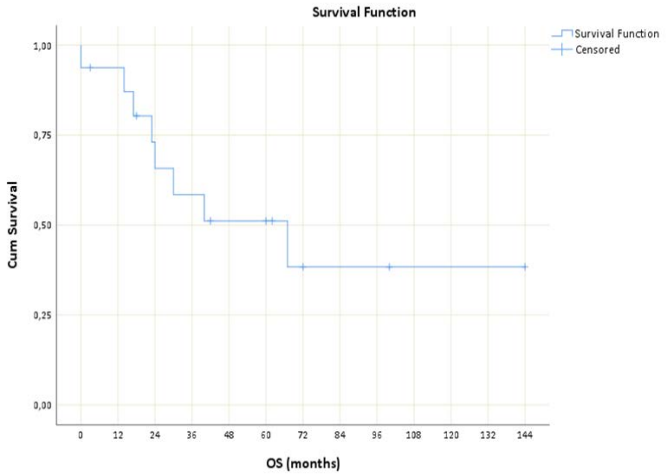


**Figure 1:** Overall Survival function of patients with Pediatric malignancies.

**Table 2:** Cumulative proportion surviving at End of Interval.

| Years after surgery | OS | DFS |
|---|---|---|
| 1 | 94% | 60% |
| 2 | 73% | 53% |
| 3 | 58% | 53% |
| 4 | 50% | 41% |
| 5 | 50% | 41% |
| 6 | 40% | 41% |
| 7 | 40% | |
| 8 | 40% | |
| 9 | 40% | |
| 10 | 40% | |
| 11 | 40% | |
| 12 | 40% | |

### 3.2. Histology

The median OS of Willms, DSRCT, RMS and Other groups weren't computed because all cases are censored. The OS time of Willms group wasn't statistically different than DSRCT group, $\chi^2(3) = 1.494$ ($p = 0.222$). The OS time of Willms group wasn't statistically different than RMS group, $\chi^2(3) = 0.500$ ($p = 0.480$). The OS time of Willms group wasn't statistically different than other group, $\chi^2(3) = 0.153$ ($p = 0.696$). The OS time of DSRCT group wasn't statistically different than RMS group, $\chi^2(3) = 1.477$ ($p = 0.224$). The OS time of DSRCT group wasn't statistically different than other group, $\chi^2(3) = 0.490$ ($p = 0.484$). The OS time of RMS group wasn't statistically different than other group, $\chi^2(3) = 0.831$ ($p = 0.362$) (Figure 2).

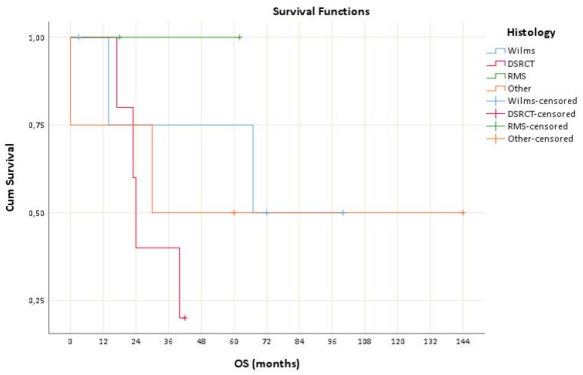


**Figure 2:** Overall Survival function of patients with Pediatric malignancies (Willms *vs.* DSRCT *vs.* RMS *vs.* Other).

The median DFS of Willms, DSRCT, RMS and Other groups weren't computed because all cases are censored. The OS time of Willms group wasn't statistically different than DSRCT group, $\chi^2(3) = 2.824$ ($p = 0.093$). The DFS time of Willms group wasn't statistically different than RMS group, $\chi^2(3) = 0.400$ ($p = 0.527$). The DFS time of Willms group wasn't statistically different than other group, $\chi^2(3) = 0.234$ ($p = 0.629$). The DFS time of DSRCT group wasn't statistically different than RMS group, $\chi^2(3) = 2.248$ ($p = 0.134$). The DFS time of DSRCT group wasn't statistically different than Other group, $\chi^2(3) = 0.601$ ($p = 0.438$). The DFS time of RMS group wasn't statistically different than Other group, $\chi^2(3) = 1.250$ ($p = 0.264$) (Figure 3).

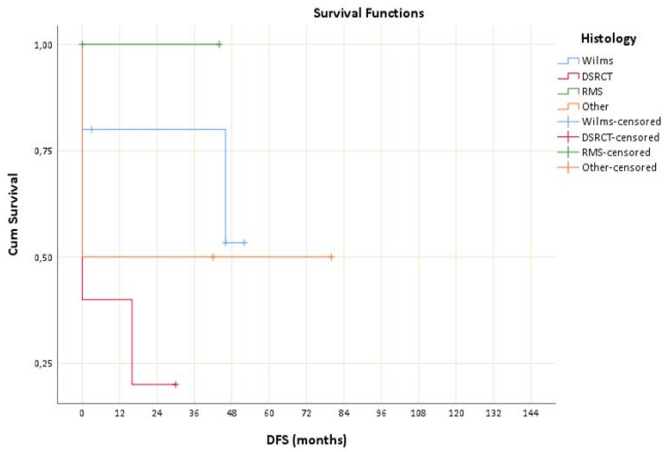


**Figure 3:** Disease-Free Survival function of patients with Pediatric malignancies (Willms *vs.* DSRCT *vs.* RMS *vs.* Other).

### 3.3. Age

The median OS of age group <13 years were 67 months (95% CI: 9-125). The median OS of age group ≥13 years was 30 months (there wasn't an observed failure time for which the lower and upper bound of the confidence interval for the KM estimate is less than 0.5). The median OS of age group <13 years wasn't statistically different than age group ≥13 years, $\chi2(1) = 0.135$ ($p = 0.713$) (Figure 4).

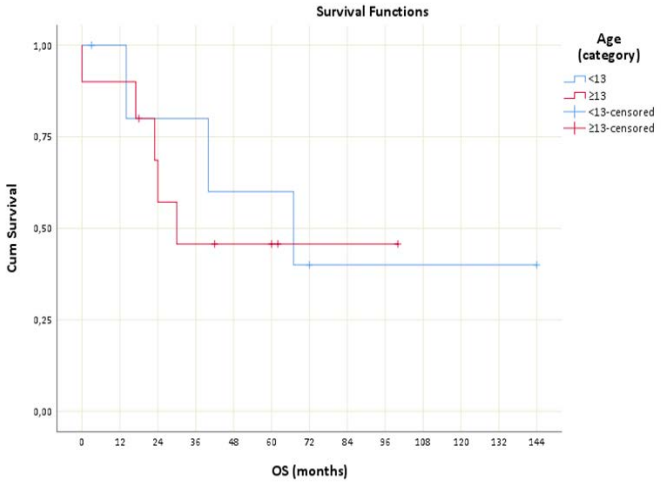


**Figure 4:** Overall Survival function of patients with Pediatric malignancies by age category.

## 4. Discussion

Our study described the twenty years' experience of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in a pediatric population with peritoneal metastasis. The results of our study support that aggressive management with selection criteria offers a safe and feasible option in children, which are the same findings from other recent options[6].

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is a surgical procedure involving the infusion of heated chemotherapy into the abdominal cavity, followed by agitation and subsequent drainage. When combined with CRS, this approach directly targets peritoneal surfaces that are poorly penetrated by traditional chemotherapy (IV) due to the peritoneal-plasma barrier. This method enhances local drug concentration and eliminates microscopic residual disease[7]. As a result, HIPEC has become an integral part of treatment protocols and is now routinely considered for adult peritoneal carcinomatosis or sarcomatosis.

However, data on hyperthermic intraperitoneal chemotherapy use in pediatric patients with peritoneal malignancies remain scarce, limited to single-arm studies, case reports and single-institution case series. The lack of large patient cohorts means there are no multicenter randomized controlled trials (RCTs) evaluating HIPEC's efficacy in children. Additionally, patient selection is highly restrictive: candidates must have resectable tumors, normal organ function and no distant metastases, though the acceptability of limited liver or lung metastases remains debated in adult cases[8].

Peritoneal malignancy in children most often occurs when a tumor breaches the organ capsule, either due to intraoperative spillage during incomplete resection, hematogenous spread or direct local invasion by malignant peritoneal tumors. The majority of cases in the literature of children population are DSRCT or Wilms tumors and same results are observed in our study in which the 50% of cases are DSRCT and Wilms tumors[9-12].

Pediatric peritoneal malignancies usually manifest as peritoneal sarcomatosis in comparison of peritoneal carcinomatosis which occur more frequently in adults[13,14]. In our study more patients (12/16) presented as sarcomatous and the other 4 cases are from colon (1), ovarian (2) and mesothelioma (1).

The survival results in our study are very optimistic with a 5-year survival rate of 50% especially in low PCI patients and without evidence of secondary deposits in Liver or Lungs.

The morbidity was observed in 20%-40% of adult cases compared to substantially reduced rates in pediatric patients. In our group the morbidity rate is 25%. Limitations of our study include various histological types, few cases of each study due to the rare incidence in children.

The establishment of an international pediatric hyperthermic intraperitoneal chemotherapy database-incorporating both retrospective and prospective patient data-would significantly advance future research and clinical practice in this field. While a Belgian hospital currently maintains such a registry (https://clinicaltrials.gov/ct2/show/NCT01617382, accessed 30/03/2023), its global uptake remains unclear. The PSOGI (Peritoneal Surface Oncology Group International) registry, though valuable, focuses primarily on adult populations with appendiceal neoplasms, rare tumors and mesothelioma. While this framework could inform pediatric efforts, the unique complexities of childhood peritoneal malignancies warrant dedicated analysis.

## 5. Acknowledgment

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