MARMARA
MEDICAL JOURNAL

Original Article

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Does cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improve survival in children with desmoplastic small round cell tumors? First experiences from Turkey

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Submitted: 23.11.2024 **Accepted:** 19.12.2024

ABSTRACT

Objective: Desmoplastic small round cell tumor (DSRCT) is a rare form of highly aggressive sarcoma and despite multimodal therapy, mortality still remains high. The aim of the study is to review our experience in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in children with DSRCT.

Patients and Methods: A retrospective review of patients with DSRCT followed in our institution between January 2020-January 2024 was performed. Demographics, radiological imaging, histopathology results, cytogenetic analyses, chemotherapy/radiotherapy protocols, operative data and outcomes were analyzed.

Results: Three patients with DSRCT were identified. The median age was 13.3 years (12-16 years). HIPEC was performed after CRS in two patients, while HIPEC procedure could not be applied in one patient with unresectable tumor. One patient underwent reoperation/re-HIPEC for recurrence after seven months. One patient had the diagnosis after complete removal of the tumor. Patient required peritonectomy and HIPEC as a second operation due to peritoneal recurrence. The patients who underwent CRS and HIPEC are still alive for 33 and 34 months since initial diagnosis, nevertheless the patient who had an unresectable tumor died after 8 months.

Conclusion: Cytoreductive surgery and HIPEC may be considered as a safe and feasible treatment option in children with DSRCT in experienced centers.

Keywords: Desmoplastic small round cell tumor, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, children

1. INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare aggressive sarcoma that typically affects pediatric and young adult patients [1]. Based upon the data obtained from experienced referral centers, the disease has a 90% male predominance and patients present at a median age of 19 years [2]. Typical histologic appearance was first described by Gerald and Rosai in 1989, characterized by nests of small round blue cells separated by desmoplastic stroma [3]. During cytogenetic research, Ladanayi and Geraldi described a unique chromosomal translocation (11;22) (p13;q12) involving *EWSR1-WT1* fusion protein which distinguishes DSRCT from other sarcomas [4]. Demonstration of this pathognomic translocation with an open or percutaneous biopsy is very essential in workup to establish an accurate diagnosis [5]. DSRCT manifests itself as large intraabdominal masses as well as widespread tumor implants implanted in the visceral and parietal peritoneum [5]. The reason why DSRCT have such a heavy tumor burden at the time of presentation is that no obvious symptoms are observed until the peritoneal surfaces are completely infiltrated with tumor, disrupting resorption and causing ascites. The spread of malignancy to the peritoneal surface is a situation that creates difficulties in the treatment of the disease [5]. Despite multimodal therapy including agressive CRS, high dose chemotherapy and whole abdominal radiotherapy (WART) survival remains poor in

How to cite this article: Karadeniz Cerit K, Eker N, Karagozlu Akgul A, et al. Does cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improve survival in children with desmoplastic small round cell tumors? First experiences from Turkey. Marmara Med J 2025; 38(1): 29-35. doi: 10.5472/marumj.1627763

ISSN: 1309-9469

DSRCT, patients develop disease recurrence or die within three years; 5-year overall survival rates have been reported 18.1% in a recent SEER analysis [1,6].

Even if the entire macroscopic tumor is surgically removed with traditional treatment methods, there is a possibility of microscopic residual tumor cells remaining [5]. HIPEC is a surgical procedure described as the infusion of heated chemotherapeutic agents into the abdomen, agitation of the abdomen and subsequent evacuation. It was thought that the combination of CRS and HIPEC could be a solution to the difficulty experienced in penetration of traditionally administered intravenous chemotherapeutic agents due to the peritoneal-plasma barrier [7]. Since, most patients die due to peritoneal recurrence; in these circumstances, CRS and HIPEC can be considered as an appropriate treatment option in children as well as in adult patients [8,9]. The aim of this study is to review our experiences in CRS and HIPEC in two patients with DSRCT and to share its safe application in children, even in recurrence and renal failure.

2. PATIENTS and METHODS

Ehical approval for this study was obtained from the Marmara University School of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 09.2023.1316). Consent for study participation was obtained from all patients or their guardians. We performed a retrospective review of patients who were followed with a diagnosis of DSRCT from January 2020 to January 2024. The patients' demographic data, radiological imaging, histopathology results, cytogenetic analyses, chemotherapy/radiotherapy protocols, surgical procedures/duration and outcomes were analyzed. Imaging of the abdomen with ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and chest CT scan and/or total body positron emission tomography (PET) scan were performed in all patients. Extraabdominal metastases (lung, liver, inguinal lymph nodes) were diagnosed according to the radiological imaging.

Degree of tumor burden is measured by peritoneal cancer index (PCI). During surgery PCI scores were calculated based on the evaluation of the location and size of the tumor [10]. All patients were staged according to the MD Anderson Cancer Center DSRCT staging criteria [5,8]. Completeness of peritoneal cytoreduction were evaluated and graded with score system described by Sugarbaker, as follows: CCR-O, if no visible residual macroscopic disease; CCR-1, if residual disease smaller than 2,5 mm; CCR-2, if residual disease between 2,5 mm and 2,5 cm; CCR-3, if residual disease greater than 2,5 cm. Surgical operations performed as CCR-O or CCR-1 can be defined as a macroscopically complete cytoreduction [11].

Once CRS and peritonectomy are completed, subsequent HIPEC procedure begins. HIPEC was applied for 60 minutes at 41^{0}C using cisplatin at a dose of 100 mg/m^2 [8]. Inflow and outflow catheters are placed and connected to a circuit containing perfusate. There are temperature probes at the distal ends of the inflow and outflow catheters, to monitor equal distribution of perfusate and protection of the liver from excess hyperthermia. An apparatus that ensures equal distribution of perfusate by carbondioxide insufflation is placed in the left quadrant. The abdomen was temporarily closed, and circulation was started. Central and intra-abdominal temperature monitoring was performed regularly [12].

3. RESULTS

During this period, three patients with a diagnosis of DSRCT were followed and treated in our institution. The median age of the patients, all of whom were male, was 13.3 years (12-16 years). Biopsy was performed in two patients, however in one patient the diagnosis was made after removal of the tumor. The diagnosis was confirmed by demonstrating the presence of translocation (11;22) (p13;q12) and EWSR1-WT1 fusion protein.

Two patients who underwent biopsy for diagnosis received neoadjuvant chemotherapy, the other one received adjuvant chemotherapy. According to the protocol of American Intergroup POG-CCG Ewing's trial (POG-9354/CCG-7942) the patients received alternative therapies [13]. In patients with relapse, treatment had been rearranged. The clinical characteristics of patients and details of the treatment are summarized in Table I.

Patient 1

A 12-year-old male patient presented with a huge abdominal mass. Main tumor measuring 8x10 cm, extensive free fluid in the abdomen and widespread tumor implants covering peritoneum were observed in abdominal CT imaging (Figure 1). In thorax CT imaging, several lesions in soft tissue density were detected in the anterior mediastinum. PET scan imaging revealed a mass located in the posterior region of the stomach, extending from midline to splenic hilus, several lesions in the anterior mediastinum, and peritoneal involvement. After diagnosis is confirmed, the patient received neoadjuvant chemotherapy and 20% regression in the size of the mass was observed. However, for the decision of CRS and HIPEC, the residual mass in the mediastinal region must also be negative for malignancy. Therefore, thoracoscopic sampling was performed for the residual mediastinal lesion and negative malignancy was confirmed. Neverthless, during surgery it was determined that the main tumor in the abdomen had a complete invasion to the spleen and posterior region of the stomach. Furthermore, widespread tumor implants were observed in gastrocolic ligament, omentum, transverse colon, the liver and the entire peritoneum. Even the stomach, spleen, pancreas, colon, omentum and the entire peritoneum were removed, it was concluded that residual tumor will remain in the retroperitoneal area, adjacent to the liver and paraesophageal region. Based on these findings the tumor was considered as unresectable. The patient died during oncological follow-up after eight months.

Table I. *Patient characteristics, treatment and outcome*

Patient	*Age (years)/ Gender Presentation (Diagnosis)*	*Neoadjuvant chemotherapy IE/VAC/ VDC*	*Surgical procedure/PCI/CCR (Operating time)*	*HIPEC*	*Postoperative adverse events*	*Adjuvant chemotherapy*	*RT*	*Status*
1	12/M Abdominal distention (Trucut biopsy)	10 cycles	Unresectable/PCI:21/(-) (6 hours)	No	-	8 cycles +Metronomic therapy	WART (30 Gy)	DOD (8 months)
2	13/M Abdominal pain, weight loss, fatigue, hypertension, high creatinine values (Open biopsy)	8 cycles	Omentectomy, small-large bowel resections, pelvic tumor resection, segmental liver resection, segmental ureteral resection, partial diaphragmatic resection, peritonectomy PCI:30/CCR-0 (23 hours)	Yes	Urinary leak from ureteral anastomosis	Maintenance therapy	WART (30 Gy)	Local relapse (7 months)
			Second operation: Small and large bowel resections PCI:6/ CCR-O (16 hours)	Yes	Short bowel syndrome Long term parenteral nutrition Hemodialysis	7 cycles (VCT)		NED (9 months)
3	16/M Abdominal pain, abdominal distention, anemic appearance (No biopsy)	-	First operation: Omentectomy, complete tumor resection PCI:27/ CCR-O (4 hours)	No		16 cycles	WART (30 Gy)	Peritoneal recurrence (Persistent ascite) (8 months)
			Second operation: Peritonectomy (7.5 hours)	Yes		6 cycles (VCT)		CR (12 months)

DOD: Dead of disease/ NED: No evidence of disease/ CR: Complete remission/ RT: Radiotherapy/ WART: Whole abdominal radiotherapy
PCI: Peritoneal cancer index/ CCR: Completeness of cytoreduction
IE: (Ifosfamide 1800mg/m2/d and Etoposide 100 mg/m2/d for 5 days)
VAC: (Vincristine, Actinomycin, Cyclophosphamide)
VDC: (Vincristine 2 mg/m2/d, day 1, Doxorubicin 75 mg/m2/d, day 1, Cyclophosphamide 1200 mg/m2/d, day 1)
VCT: (Vincristine, Cyclophosphamide, Topotecan)
Maintenance therapy: (Vinorelbin, Cyclophosphamide)

Patient 2

A 12-year-old male patient presented with widespread tumor masses located in aortocaval area, portal hilus, the liver and splenic flexure which were detected by abdominal CT imaging. Additionaly, tumor masses adjacent to rectum and bladder were observed. Moreover, tumor masses surrounding the distal part of both ureters which is probably the cause of bilateral grade 2-3 hydroureteronephrosis were also detected (Figure 2). After the diagnosis is confirmed, the patient received neoadjuvant chemotherapy and CRS/HIPEC procedure was performed. The patient was administered aggressive fluid replacement therapy during and after surgery. No acute kidney injury was observed postoperatively, adjuvant chemotherapy and WART were administered (Figure 3). Seven months after complete remission, patient presented with local tumor recurrence. Reoperation and re-HIPEC was planned. Due to the increased creatinine values above baseline, preparations for possible need of hemodialysis were organized. Aggressive fluid resuscitation using crystalloids (Ringer's lactate and normal saline, 1200 cc/m^2) were administered before operation to prevent additional kidney injury after HIPEC. In the postoperative period, according to the glomerular filtration ratio fluid resuscitation increased to 1500 cc/m^2. No alterations were observed at serum creatinine levels postoperatively. During surgery complete removal of the recurrent tumor was achieved, however extensive bowel resection and ileostomy were performed. Since, the volume loss from ileostomy was high, patient required long-term parenteral nutritional support. Hemodialysis was started at the third month after surgery due to increased creatinine levels and patient still continues to receive hemodialysis twice a week. Adjuvant treatment continues and patient is disease free for 9 months. He has been alive for 34 months since initial diagnosis.

Patient 3

A 16-year-old male patient presented with a 30x11 cm mass which was detected by abdominal CT imaging. The patient

had to undergo an urgent operation due to tumor rupture causing symptoms of acute abdomen. During surgery, a mass originating from omentum and extending to pelvis was detected. The mass had multiloculated structure with cystic and solid components. The mass was completely removed, however extensive hemorrhagic fluid was observed in the abdomen due to preoperative rupture. Postoperatively, thorax CT imaging revealed 3 cm pleural effusion in the left hemithorax and multiple nodules in the right lung. Based on the pathology result of the removed mass, adjuvant treatment was started. During the patient's follow-up, persistent ascite was observed in the abdomen (Figure 4). Since, malignant FDG uptake was also observed in PET images, sampling was performed considering that persistent ascite developed due to peritoneal recurrence. As the sampling of the ascite resulted as malignant, peritonectomy and HIPEC procedure were performed as a second surgical procedure (Figure 5). Patient is in complete remission for 12 months. He has been alive for 33 months since initial diagnosis.

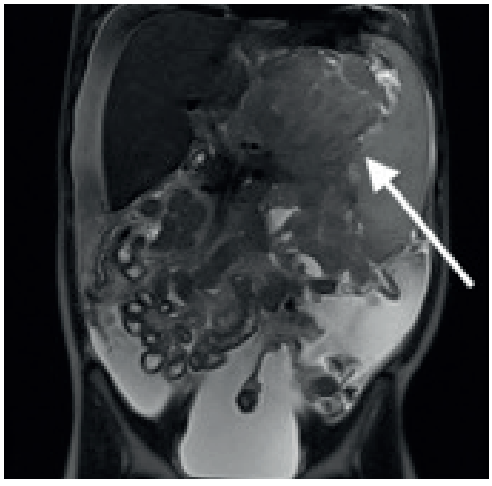

Figure 1. *CT image of the abdominal mass located in the posterior region of the stomach at presentation (Patient 1)*

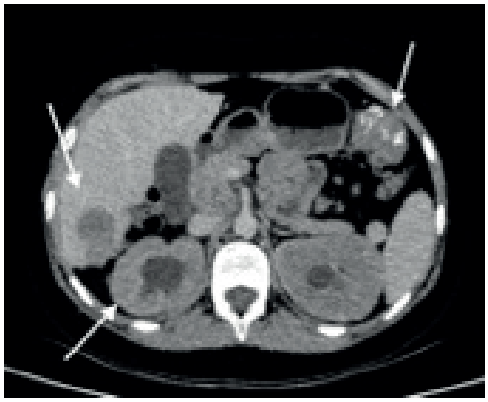

Figure 2. *CT image demonstrating multiple abdominal, pelvic, liver masses (Patient 2)*

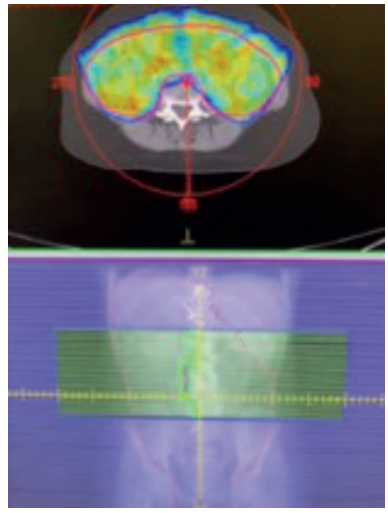

Figure 3. *Image of the whole abdominopelvic radiotherapy plan area (Patient 2)*

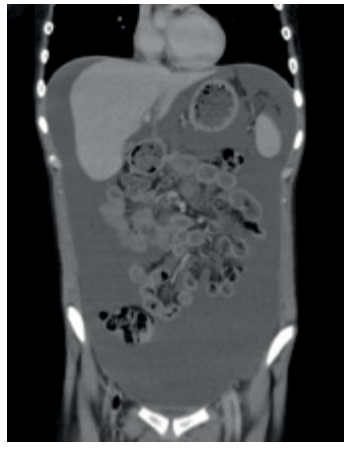

Figure 4. *CT image of the persistent resistant acid during adjuvant treatment*

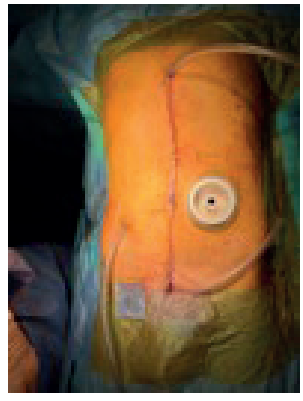

Figure 5a. *HIPEC procedure demonstrating inflow and outflow catheters*

http://doi.org/10.5472/marumj.1627763
Marmara Med J 2025;38(1): 29-35

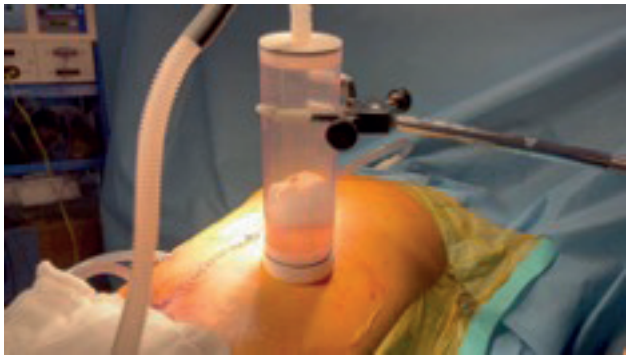

Figure 5b. *Distribution of perfusate by carbondioxide insufflation*

4. DISCUSSION

Desmoplastic small round cell tumor is a rare form of highly aggressive sarcoma with high mortality rates despite multimodal therapy including CRS, chemotherapy and radiotherapy [4]. It has been observed that microscopic residual masses are present even after gross total resection following neoadjuvant chemotherapy in DCRCT. HIPEC was predicted to be an effective additional strategy that could be applied during the continuation of the operation in these patients [14]. Since, the disease does not show clinical symptoms, patients generally present at a very advanced stage [15]. Abdominal pain, distension and discomfort are generally observed as the first complaints [15]. In our study, consistent with the literature, all patients presented with widespread lesions, accompanied by lung and liver metastasis. All patients were evaluated as stage 4 in their initial evaluation.

Promising results of the chemotherapy regimens used in 12 patients with DSRCT have been published [16], however there is no standard chemotherapy regimen or standard approach for local control of this rare disease. Although, radiological images describe widespread appereance of disease, patients should be given the chance for chemotherapy. The response to neoadjuvant chemotherapy in DSRCT generally reaches a plateau level around 4-6 months; it is not appropriate to evaluate the suitability of total surgical resection before reaching this stage. Although, most lesions do not decrease in size, a significant decrease in tumor vascularity will be observed, in addition malignant ascites also respond well to chemotherapy. According to the response to chemotherapy, aggressive surgeries in which the tumor can be completely removed will be possible [5]. Adjuvant therapy includes WART and 12 cycles of irinotecan and temozolomide [17]. Since, DSRCT is a tumor that presents with large intra-abdominal masses as well as visceral and peritoneal widespread tumor implants, WART is a more effective treatment than locoregional radiotherapy [18]. The treatment dose in WART is 30 Gy in 1.5-1.55 Gy fractions with or without focal additional doses [17]. The use of intensity-modulated radiation therapy (IMRT) in treatment reduces the doses to adjacent normal organs and minimizes side effects. It also provides more homogeneous dose distribution on peritoneal surfaces [19]. In our study, two patients had good response to chemotherapy protocols and WART. However, in one patient the expected regression in tumor size was not achieved, and CRS/HIPEC could not be applied.

The approach of surgical resection of more than 90% of the tumor burden accompanied by multiagent chemotherapy treatment is the basis of the treatment that has a positive effect on survival in DSRCT [20]. Lal et al., reported in their study that while the 3-year survival rate was 58% in patients who could undergo total surgical resection, this rate was observed to be 0% in patients who could not undergo total surgical resection and only received chemotherapy and radiotherapy [21]. When the data of 26 DSRCT patients who underwent surgical resection and HIPEC after neoadjuvant chemotherapy were evaluated, it was emphasized that complete cytoreduction determined the outcomes in survival. Even though, HIPEC accompanies the operation, a negative impact of incomplete cytoreduction on survival was observed [22]. In our study, we have also observed that in cases of unresectable tumors, there was no chance of survival despite applied chemotherapy regimens and WART.

In a Phase 1 clinical study published in pediatric patients; HIPEC using cisplatin at a dose of 100 mg/m2, which has limited toxicity, has been shown to be a reliable method with a risk of grade 3 renal failure [14]. However since cisplatin is a nephrotoxic agent, acute renal failure is one of the most important complications that may be encountered in short term. Hayes-Jordan et al., reviewed CRS and HIPEC results applied to 20 pediatric sarcoma patients in a Phase 2 trial [23]. Patients with liver or renal dysfunction, cardiovascular contrindications to general anesthetic, detectable fluorodeoxyglucose (FDG)-avid disease by PET scan imaging outside the abdominal cavity were not included in this clinical trial [23]. Although, it was emphasized that it is appropriate to use HIPEC based on a protocol, however one patient with renal failure underwent reoperation and re-HIPEC due to local recurrence in our study. Since, the indications for HIPEC application in children are still a controversial issue, we think that this risk can be taken by sharing possible surgical complications and risk of dialysis with the family, considering that these patients have no chance of survival if they are not operated.

Although, DSRCT is a chemosensitive tumor, recurrence after resection is very common [20]. In a Phase 2 trial which included highly selected subset of patients; it was particularly emphasized that effective local control can be achieved in DSRCT patients without liver disease and no recurrence of peritoneal disease is observed during the observed follow-up period [23]. In addition, if a patient included in this trial has liver metastases, liver masses must be resectable during CRS and HIPEC or without metabolic activity on PET scan. However, another issue highlighted in the study is that 33% of DSRCT patients without any liver or portal disease developed disease in the inguinal lymph nodes, lung and liver parenchyma, although there was no peritoneal recurrence [23]. This suggests that besides to effective CRS, HIPEC and WART treatment; more advanced systemic chemotherapeutic agents should play a role in prevention of tumor recurrence and ensuring local control in DSRCT patients. In our study the

patient who presented with extensive abdominal lesions as well as liver metastases, underwent CRS including liver resection. Although, complete cytoreduction (CCR-O) and HIPEC were performed, he presented with local tumor recurrence after 7 months. To reoperate a child who had undergone CRS, HIPEC and WART was a very complicated procedure. If a decision for reoperation and re-HIPEC for tumor recurrence is given, surgeon should be aware of the challenges and must be prepared for possible complications due to hostile adhesions.

There are differences in surgical approach, cytoreduction and HIPEC technique in children with DSRCT compared to adult patients with carcinomatosis. Low anterior resection of the rectum, splenectomy and segmental bowel resection may be required in most cases with carcinomas [24]. Hayes-Jordan et al., emphasized in their study that DSRCT is more nodular than carcinoma and much less infiltrative especially in small bowel mesentery and pelvis region, since superficial dissection is possible from the jejunal and ileal mesentery and there is no need for small bowel resection. Likewise, dissection of pelvic tumors surrounding the the ureters, bladder and rectum is often possible [24]. Although, Hayes-Jordan stated that DSRCT lesions were less infiltrative and could be removed superficially, unfortunately operative findings of the patients in our study were not similar. In the first patient complete invasion to adjacent organs made tumor resection impossible and it was concluded that the tumor was unresectable. In the second patient to achieve complete cytoreduction (CCR-0); partial resection of the both ureters infiltrated with tumor, small bowel resection and segmenter colon resection were required.

Cytoreductive surgery and HIPEC is an aggressive surgical procedure with long operating times, serious blood loss and high morbidity rate. All factors such as receiving multi-agent neoadjuvant/adjuvant chemotherapy, CRS, HIPEC and WART have a cumulative effect on morbidity [20]. It is important to be aware of situations such as gastroparesis, intestinal obstruction due to sclerosing peritonitis, malnutrition requiring parenteral nutrition and hemorrhagic cystitis that may be encountered in the long term. It was reported that long-term complications occurred one year or later after surgery, moreover hospitalization and additional procedures may be required due to these complications in these children [20].

Since, HIPEC can only be applied in centers with the requisite expertise and given the extreme rarity of the disease, the data on HIPEC use in children with DSRCT is unfortunately limited [24,25]. The reports of HIPEC in children likely represent a highly selected group of patients, therefore we believe that it is essential to share experiences even with small number of patients. HIPEC and re-HIPEC procedures were successfully performed in two patients in our study. We believe that HIPEC procedure can be successfully applied with a multidisciplinary approach, even in patients with renal failure by taking precautions such as regulating fluid therapy before and after surgery and making preparations for the possible need for hemodialysis.

Conclusion

Although, there is insufficient evidence regarding the long-term survival outcomes, HIPEC may be considered as a treatment option for selected patients regarding the poor prognosis of DSRCT.

Compliance with Ethical Standards

Ethical approval: Ehical approval for this study was obtained from the Marmara University School of Medicine Non-Interventional Clinical Research Ethics Committee (approval number: 09.2023.1316). Consent for study participation was obtained from all patients or their guardians.

Conflict of interest: The authors declare that there is no conflict of interest.

Financial support: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contribution: KKC and NE: Concept and design, NE, AKA, DG, ONT, ACB and AE: Data collection and processing, KKC, NE, AKA, DG, ONT, ACB, AE and GK: Analysis or interpretation, KKC, NE, AKA and DG: Literature search, KKC, NE and AKA: Writing the manuscript. All authors approved the final version of the manuscript.

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