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SARCOMAS (SR PATEL, SECTION EDITOR)

Cytoreductive Surgery Followed by Hyperthermic Intraperitoneal Chemotherapy in DSRCT: Progress and Pitfalls

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Abstract Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) is an approach for local control of desmoplastic small round cell tumor (DSRCT). DSRCT is a rare sarcoma which presents with multiple intra-abdominal masses. Overall survival has been 15–30 %. Because of the poor prognosis of DSRCT, novel treatment strategies were necessary. Cytoreductive surgery (CRS) and HIPEC has been recently trialed as part of multimodality therapy in DSRCT. CRS and HIPEC allows complete resection of the sometimes hundreds of intra-abdominal tumor implants, followed by the delivery of hyperthermic cisplatin for 90 min at approximately 41 °C. HIPEC is thought to enhance microscopic control of abdominal DSRCT, after surgical resection, and prevent or prolong recurrence. Here, the background of DSRCT, the multimodal treatments available, and the progress and pitfalls of CRS and HIPEC in DSRCT are reviewed.

Keywords Desmoplastic small round cell tumor (DSRCT) · Sarcoma · Abdominal · Pediatric · Adolescent-young-adult (AYA) · Metastatic

Introduction

Desmoplastic small round cell tumor (DSRCT) was a relatively unknown tumor that was considered by most clinicians to be an aggressive rare sarcoma that was lethal. Identifying the pathology and characteristic translocation was of key importance to developing any treatment strategies. In 1989, DSRCT was first described as a unique pathologic entity [1]. Because nearly all of these patients were considered stage 4 because of innumerable abdominal tumors, palliative care only was previously offered. The exact incidence is unknown. But fewer than 200 cases can be found published in the English language. The survival is estimated only at 15 to 30 % [1–3].

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Diagnosis and Staging of DSRCT

The extent of disease seen on initial imaging includes many lesions in every portion of the peritoneal cavity. The most common areas are the omentum, right diaphragm, and pelvis. The splenic hilum and various small bowel and colon mesenteric implants are also common. Retroperitoneal disease is very uncommon. In most cases, the disease seen on computed tomography (CT) scan or MRI underestimates the extent of the diseases. One to 2 mm metastasis and "sheets" of tumor in confluence is a common intraoperative finding. Metastatic disease outside of the abdominal cavity is common in the mediastinum, pleura, supradiaphragmatic lymph nodes, lung, and bone.

A large tumor burden exists at diagnosis, and few symptoms are present until the peritoneal surfaces are infiltrated with tumor and overwhelm the peritoneum, therefore impairing resorption of peritoneal fluid and causing ascites. Abdominal distension and discomfort is the usual presenting symptom. Patients can also have pain and constipation.

The original pathological description was by Gerald and Rosai [1, 2]. They described not only the characteristic translocation but the histologic appearance. Nests of small round blue cells can be seen separated by desmoplastic stroma (Fig. 1). The translocation (11:22) (p13:q12) and the fusion

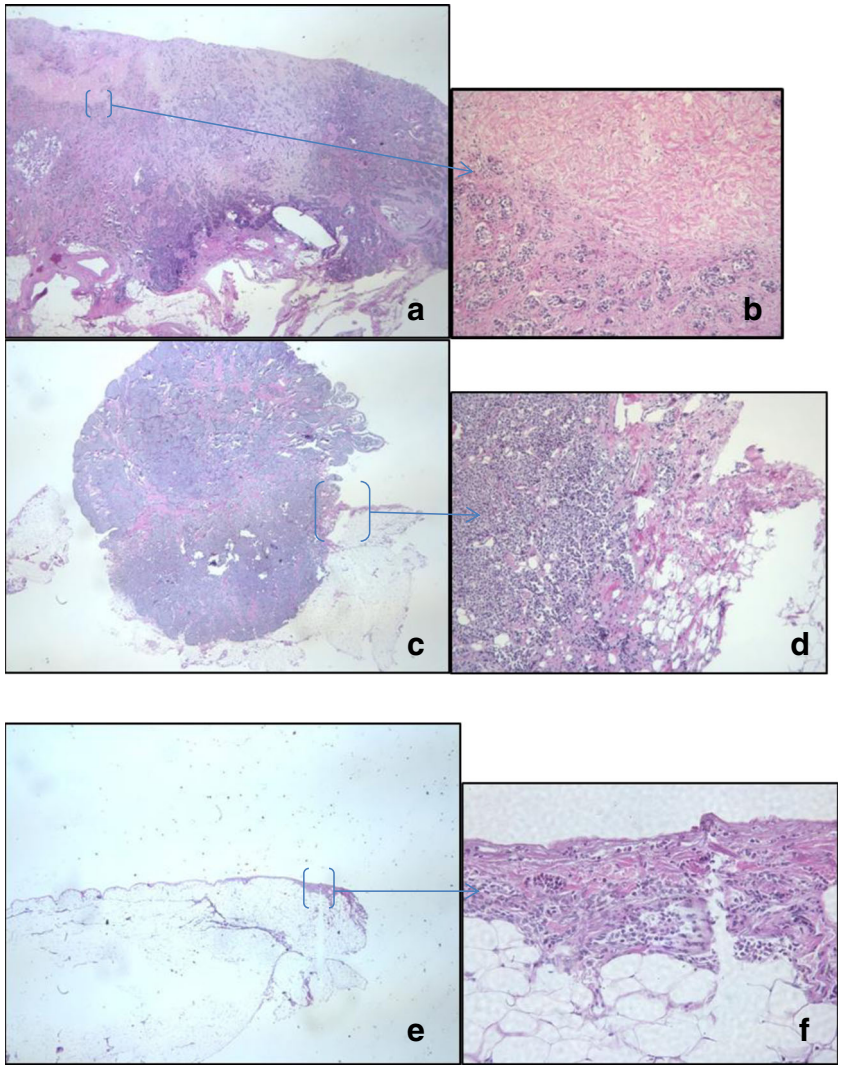

Fig. 1 **a**–**f** Microscopic hematoxylin and eosin stains of DSRCT peritoneal metastasis. **a**, **c**, and **e** are 1×. **b**, **d**, and **f** are 10×. **a**, **b** Omental implant with magnified view of pink desmoplastic reaction and islands of small round cell tumor. **c**, **d** Peritoneal DSRCT implant from right flank peritoneum. Magnification shows infiltration into surrounding normal peritoneum. **e**, **f** Normal-appearing peritoneum with microscopic evidence of DSRCT infiltration into adipose tissue and peritoneum

protein of Ewing's sarcoma (EWS) and Wilms' tumor (WT-1) make the diagnosis [1–3]. Confirming this translocation to make the diagnosis of DSRCT by percutaneous or open biopsy is necessary.

If the EWS translocation is not identified, the diagnosis becomes challenging. One author describes the desmin reactivity and cytokeratin staining can be seen in either blastemal predominant Wilms' tumor or DSRCT. Detection of an EWSR1-WT1 rearrangement and selective WT1 carboxy-terminus immunoreactivity (characteristic of DSRCT) or dual immunoreactivity for the WT1 amino-terminus and carboxy-terminus (characteristic of WT) remain the most discriminating diagnostic tools [4].

Sometimes the EWS-Fli translocation is not present, presenting a diagnostic dilemma. Desmin reactivity and coexpression of desmin and cytokeratin are historically associated with DSRCT. These features can be seen in either DSRCT or blastemal-predominant WT. In these challenging cases, detection of an EWSR1-WT1 rearrangement and selective WT1 carboxy-terminus immunoreactivity (characteristic of DSRCT) or dual immunoreactivity for the WT1 amino-terminus and carboxy-terminus (characteristic of WT) remain the most discriminating diagnostic tools, according to a recent report [4]. Percutaneous or open biopsy of the lesion should be evaluated by cytogenetics to confirm the characteristic translocation and WT1 fusion.

The most recent epidemiology data from SEER, in 172 cases, shows peak incidence between ages 20 and 24 years old. Age-adjusted incidence rate for blacks was 0.5 cases/million and for whites was 0.2 cases/million (P=0.037). There was no statistically significant difference in survival based on gender or ethnicity [5]. There was a statistically significant survival advantage for patients who received radiation after surgery compared to those who did not (HR 0.49; 95 % CI 0.30, 0.79).

The age of presentation is typically age 5 to 30 years, and 85–90 % of the patients are male. Overall survival of DSRCT in 5 years can be estimated as low as 15 % [6]. Large masses, in

addition to visceral and parietal seeding of the peritoneum, are typical in DSRCT. The dissemination of DSRCT throughout the abdominal cavity is characteristic. Because of this, almost all patients are considered stage 4 at diagnosis. It is rare for a patient to present with a single mass or one or two masses. This only occurs when the mass is found incidentally at the time of another operation or diagnostic radiologic exam for another entity. Usually vague abdominal pain brings this to the attention of the patient and prompts imaging examinations.

On initial imaging, typically, computed tomography (CT) scans are done. MRI and ultrasound can also be helpful. On CT scan or MRI, usually multiple nodules can be seen, making the diagnosis of DSRCT highly suspicious. The most common site of initial organ metastasis is usually the liver. The lung pleura and mediastinum are the next most common locations for metastasis. Lymph node enlargement in the groin and neck can also be seen. Therefore, positron emission tomography (PET) scan imaging may be a helpful adjunct to evaluate distant metastasis at the time of staging [7].

The organ of origin of DSRCT is unknown. A microscopic view of this peritoneal based sarcoma shows infiltrates into the hypovascular peritoneum, even when grossly visible disease is barely apparent (Fig. 1). In Fig. 1e, no gross disease was evident in the peritoneum. It has been our observation that of 91 cases, all but one had tumor in the omentum (as well as other sites). However, Fig. 1f clearly shows microscopic infiltrate. The omentum could be the organ of origin with metastasis to the peritoneum. Figure 1a shows omental DSRCT, and Fig. 1b demonstrates peritoneal implants from the same child.

When looking grossly at the appearance of DSRCT nodules, it is clear they are different from carcinomatosis (Figs. 2, 3, and 4). The nodules are more white color in appearance, with little vasculature, suggesting the reason chemotherapy has only a limited effect in reducing tumor size. Also, the nodules are peritoneal based. The peritoneum is a very poorly

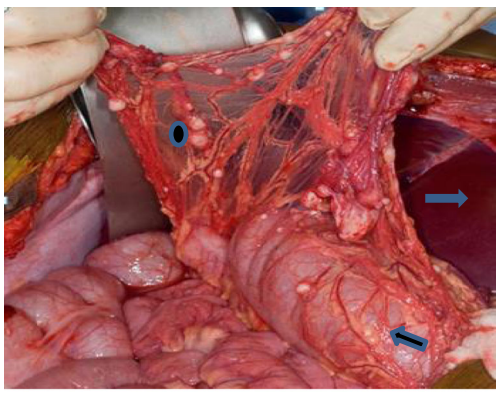

Fig. 2 Omentum

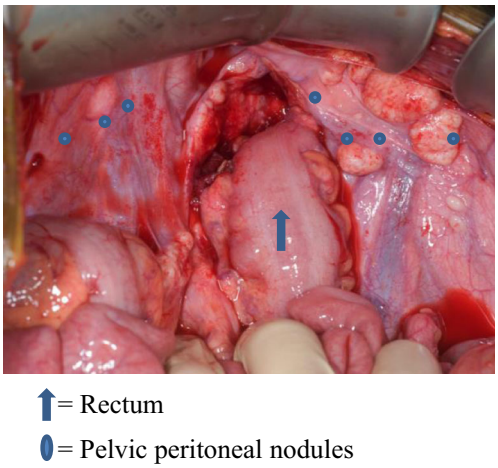

Fig. 3 Pelvis DSRCT

vascularized organ, and therefore, effective penetration of chemotherapy is impaired. Another confounding factor to preventing successful cure is the size of the lesions is often 1–2 mm and therefore evades routine diagnostic imaging. This may lead to a false sense of resolved disease, resulting in discontinuing chemotherapy and witnessing of rapid tumor regrowth. At some point in the therapy, an operative "second look" may be required.

New Staging

Presently, there is no formal staging system for DSRCT. If over 90 % of DSRCT patients present with multiple intra-abdominal metastasis, all patients cannot be stage 4, which is what they would be categorized as in the present American Joint Committee on Cancer (AJCC) sarcoma staging system. Since we do not know the organ of origin, whether these are multifocal, or metastatic tumor is unclear. In a proposed (this staging system has not been validated) new staging system by DSRCT researchers at the University of Texas MD Anderson Cancer Center (MDACC), stage 1 tumors would be limited to the omentum; stage 2 are patients with peritoneal disease only, regardless of the number of metastasis; stage 3 patients have liver metastasis; and stage 4 patients have disease outside of the abdominal cavity and/or nodal metastasis. Of 56 DSRCT patients evaluated at MDACC, the median age was 18 years (3–53 years). Median follow-up was 28 months. Staging was done at diagnosis; however, all patients underwent cytoreductive surgery and HIPEC. Median overall survival was 31.8 months. With the proposed new staging, stage 1 patients had a 3-year overall survival of 100 %, stage 2 71 %, stage 3 40 %, and stage 4 31 %. Multivariate analysis showed stage 3 or 4 patients had a higher risk of death or experience disease recurrence compared with stage 1 or 2 patients (HR=2.33 with a 95 % CI of 1.12 to 4.84, P=0.024). Patients without extra-abdominal disease had a lower risk of death or experiencing disease recurrence compared to those with distant metastases (HR=0.31, 95 % CI of 0.12 to

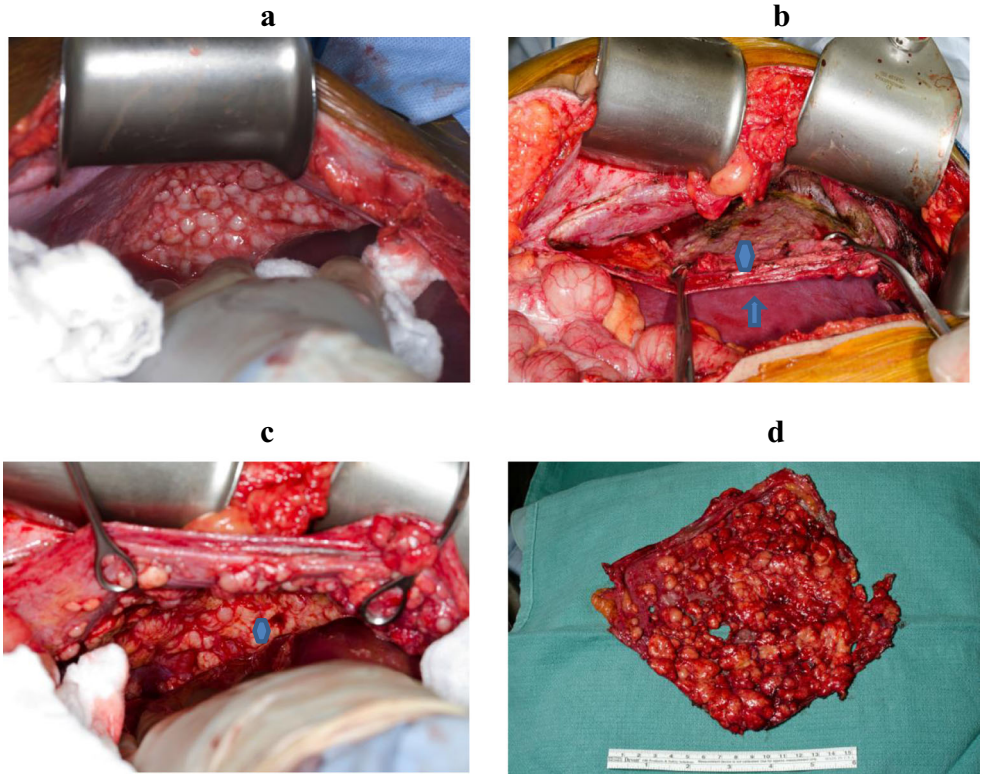

Fig. 4 **a** Looking into the right upper quadrant of the abdomen at the right diaphragm surface. **b** Peritoneum of the diaphragm being resected sparing the diaphragm muscles. ⬆ liver; diaphragm muscle; ⬡ peritoneum of diaphragm. **c** Diaphragm peritoneum from under surface. **d** Complete resection of diaphragm peritoneum, sparing the muscle, with hundreds of tumor nodules resected

0.79, P=0.014). Patients with incomplete resection (HR=4.79, P=0.03) had a higher risk of death, and patients without liver disease (HR=0.43, P=0.046) had a lower risk of death. This proposed new staging system requires at least 100 patients to validate and continues to be under review.

Surgical Treatment of DSRCT

Complete surgical resection, including cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) for carcinomatosis, is standard therapy for appendical and colon carcinoma, among others [8–15]. Complete cytoreduction and HIPEC have been found to improve survival in many studies of carcinomatosis [9, 13–15]. Intraperitoneal therapy is currently the recommended approach in carcinomatosis of ovarian, mesothelioma origin also [2, 16–22]. This same principle was applied in the initial study of HIPEC in DSRCT. In the early late 1990s, when evaluating a patient with DSRCT, surgeons were reluctant to offer surgical resection in the face of enormous disease burden in the abdomen and no known hope for disease control or cure. As in carcinomatosis, HIPEC can provide control of microscopic disease in DSRCT after resection of 100 % of gross disease. In the context of a prospective randomized trial, gastric cancer patients with carcinomatosis underwent cytoreduction accompanied by normothermic or hyperthermic Mitomycin C. The overall 5-year survival of surgery alone or normothermic or hyperthermic perfusion was 42, 43, and 61 % respectively [2]. In ovarian carcinoma, a national prospective randomized trial identified patients undergoing complete or near-complete cytoreduction and intraperitoneal, vs. intravenous cisplatin and paclitaxel, found statistically significant superior survival in the intraperitoneal chemotherapy group [22].

The partial response to neoadjuvant chemotherapy in DSRCT is clearly an important component to complete surgical resection and HIPEC and successful local control. In a report of the impact of complete surgical resection of DSRCT, without HIPEC, LaQualgia and colleagues found a 3-year overall survival of 58 % with complete resection and 0 % when resection was not done and the patients were treated with chemotherapy and radiotherapy alone [6].

A French group also reported improved outcomes with complete surgical resection and postoperative radiation and chemotherapy. This was not a randomized trial, but they did not find a survival advantage to HIPEC [23•]. Twenty-three of 27 patients underwent surgery, 12 (52 %) experienced complete removal of all macroscopic disease, 5 (21.7 %) received additional intraperitoneal chemotherapy, and 7 (30 %) received postoperative whole abdominopelvic radiotherapy (WAP RT). With a median follow-up of 59.9 months, the median survival was 37.7 months, and the median disease-free survival was 15.5 months. In patients without extraperitoneal disease, a multimodal treatment combining systemic chemotherapy, complete macroscopic resection, and postoperative whole abdominal radiation therapy could enable prolonged survival. No benefit of surgery was

demonstrated for patients with extraperitoneal metastasis [23•]. The value of associated HIPEC in addition to cytoreductive surgery for DSRCT remains controversial.

At the author's institution, cytoreductive surgery and HIPEC was begun in children with DSRCT. The authors' group provided the first case report of HIPEC in children [24]. Previously, there were no prospective trials of HIPEC in children. The results of a phase 1 trial of cytoreductive surgery and HIPEC in children proved safety with the maximum tolerated dose (MTD) being 100 mg/m^2 intraperitoneally for 90 min at 41 °C. Dose-limiting toxicity (DLT) was renal insufficiency and renal failure. There were no grade 4 or 5 toxicities. There were 10 hematologic and 20 non-hematologic grade 1 or 2 toxicities. In the two patients for whom dose was reduced, creatinine levels did not exceed grade 3 but creatinine elevations were over 100 % of baseline [25••]. There were no surgical mortalities. There were no intraoperative complications. One patient required readmission and non-operative management of a bowel obstruction. One patient had a severe wound infection which required operative washout and lengthened hospital stay. One patient suffered an asymptomatic cardiomyopathy found on postoperative screening echocardiogram. This resolved with beta blockade and may have been secondary to tumor necrosis factor effect on the cardiac musculature from resection of a large amount of tumor. (This is the patient who had 2.5 lb of tumor resected.) Two years after enrollment, preliminary outcomes were reported. Five of eight patients (62 %) remained disease free for at least 2 years. Two (25 %) recurred before 6 months and died, and one (12 %) recurred at 6 months and remained alive with disease for almost a year before death. Four of five patients who had a surgical CR had disease previously deemed unresectable at outside institutions [25••].

Pitfalls

After this experience with renal failure in our Phase I trial, we halted HIPEC procedures until a complete analysis of the potential reasons for renal failure were investigated. Twenty-two outcome measures were evaluated in 54 adult and pediatric patients (ages 3 to 53 years) and in 58 HIPEC procedures. These included types and amount of intravenous fluid, pre-, intra-, and postoperatively, types of chemotherapy, amount of blood transfusions, albumin delivery, and others. Thirty-seven (37/58) of the HIPEC procedures were done in patients 18 years of age or younger. The most common tumor type was DSRCT (N=35) [rhabdomyosarcoma (N=6), mesothelioma (N=5), Wilms' tumor (N=2), liposarcoma (N=2), and other rare tumors (N=8)]. There were no mortalities secondary to the surgery. Overall, grade III renal toxicity occurred in 14 % (8/58) and grade IV toxicity required dialysis in 5 % (3/58) of HIPEC procedures. Patients who had preoperative hydration at greater than maintenance intravenous rate had less renal toxicity. This was statistically significant on univariate and multivariate analysis. On univariate and multivariate analysis, patients who had intravenous sodium thiosulfate administered simultaneously with HIPEC had less renal toxicity compared to those who received sodium thiosulfate at the end of HIPEC. Patients who had preoperative hydration of more than 15 h had less renal toxicity (P= 0.0493), but this did not remain significant on multivariate analysis.

Timing of doses of sodium thiosulfate was not associated significantly with disease-free survival (DFS) or overall survival (OS) (P=0.09444, P=0.8019, respectively). Other variables were not significantly associated with renal toxicity. Grade III and IV toxicities were reduced to 0 % after initiation of our renal protective protocol (P=0.0012) [26•]. Presently, our renal protective protocol includes intravenous hydration, in hospital the day prior to HIPEC, delivery of sodium thiosulfate 30 min into the HIPEC therapy, and aggressive postoperative hydration.

A phase 2 trial of cytoreductive surgery and HIPEC in DSRCT and other sarcomas was just completed. The results have not been published, awaiting long-term follow-up data. However, published results of outcomes of DSRCT patients only have shown that complete or near-complete cytoreduction and HIPEC prolongs survival, compared to debulking or partial surgical resection. Patients aged 5 and up underwent neoadjuvant chemotherapy, followed by cytoreductive surgery and HIPEC, adjuvant chemotherapy, and adjuvant whole abdominal radiation therapy. Patients with complete or near-complete (2.5 cm of tumor left behind that received boost radiation also) cytoreduction and HIPEC had a median survival of 60.1 months, compared to 26.7 months for those with debulking surgery and HIPEC [27]. Patients who did not have a response to neoadjuvant chemotherapy were not offered surgical resection. Survival dependent variables included disease outside of the abdominal cavity and lack of postoperative radiation therapy. Age and liver metastases (if they were resected or ablated at the time of CRS and HIPEC) did not significantly impact survival [27].

The cytoreductive surgery itself is likely the most effective local control. Figures 2, 3, and 4 show omental, pelvic, and diaphragm appearance of DSRCT intraoperatively. In Fig. 3, only a few of the more than 30 tumor nodules are highlighted. As can be seen by the diaphragm image (Fig. 4a–d), peritoneum and tumor can be removed without damaging the muscle beneath. In the authors' experience, the areas of highest lymphatic flow, the right diaphragm Morrison's pouch and pelvic peritoneum are the most common sites of peritoneal metastasis. Complete resection of the pelvic peritoneum with even less than 1-mm implants avoids recurrence. However, the longest disease-free survivors have undergone complete resection of the peritoneal disease, HIPEC, followed by adjuvant chemotherapy and whole abdominal radiation therapy.

Chemotherapy

Since its description in 1991, multimodality chemotherapy has been used. Ewing's type chemotherapy, aggressive surgery, tumor debulking, total abdominal radiation therapy, and high-dose chemotherapy followed by autologous stem cell rescue have all been used in the treatment of DSRCT, with little improvement in survival. Durable remissions remain rare [28]. Control of DSRCT with chemotherapy is most effective in children, with Ewing's type chemotherapy. Ewing's type chemotherapy is the standard because efficacy with this regimen has been demonstrated by Kushner et al. [28]. This chemotherapy is based on alkylating agents cyclophosphamide or ifosfamide along with vincristine and doxorubicin alternating with ifosfamide and etoposide. This regimen was shown to have a favorable outcome in a multidisciplinary approach in 12 DSRCT patients [28]. This chemotherapy regimen was used in combination with aggressive surgical complete excision and postoperative whole abdominal radiation, providing improved survival. With a median follow-up of 22 months, the median survival disease-free survival was 19 months. The regimen can be quite toxic, and frequent admissions for fever and myelosuppression can be expected. An alternative more tolerable outpatient regimen has been completed at MD Anderson Cancer Center [29]. This includes neoadjuvant vincristine, ifosfamide, dexrazoxane/doxorubicin, and etoposide. This is followed by aggressive surgical excision and removal of all gross disease, including 1- to 2-mm peritoneal implants. This was followed by adjuvant radiotherapy (30 Gy whole abdomen) and irinotecan and temodar for a total of 12 cycles. This regiment yielded a disease-free interval of at least 2 years. The irinotecan and temodar therapy provided an excellent quality of life with regular school attendance and participation in planned activities. This regimen continues to be used as standard treatment for DSRCT at this institution [29].

In a summary of cases treated by French oncologists, 38 patients with DSRCT were identified. Fourteen patients (37 %) were treated exclusively with systemic chemotherapy (Ewing's type), with a median survival of 21.1 months. Twenty-three patients underwent surgery, 12 (52 %) experienced complete removal of all macroscopic disease, 5 (21.7 %) received additional intraperitoneal chemotherapy, and 7 (30 %) received postoperative whole abdominopelvic radiotherapy (WAP RT). With a median follow-up of 59.9 months, the median survival was 37.7 months, and the median disease-free survival was 15.5 months. The factors predictive of 3-year overall survival were the absence of EPM, complete surgical resection, postoperative WAP RT, and postoperative chemotherapy [23•].

More recently, pazopanib has been used for relapsed DSRCT patients. In a European cooperative group study, nine DSRCT patients received pazopanib. Best response was partial response (PR) in 2/9 (22 %) patients, stable disease (SD) in 5/9 (56 %), and progressive disease (PD) in 2/9 (22 %) with a clinical benefit rate (PR+SD>12 weeks) of 78 %. Median PFS and OS were 9.2 (95 % CI 0–23.2) and 15.4 (95 % CI 1.5–29.3) months, respectively. With a median follow-up of 20 months, 2/9 (22 %) patients are still alive, and all progressed [30].

Trabectedin has been used in a case report in a patient with DSRCT. This resulted in a favorable response in a heavily pretreated young adult. Trabectedin may be a treatment option in multimodal therapy for the management of DSRCT and warrants further research to explore the impact of trabectedin in the treatment of this disease [31].

Conclusion

DSRCT is a potentially lethal disease for which a combination of chemotherapy, radiation, and aggressive surgical resection can extend survival. Because the chemotherapy is only partially effective, patients that have excellent control of their disease in the primary site, the abdominal cavity, may recur outside of the abdominal cavity and eventually succumb to their disease. Here, DSRCT is reviewed, along with HIPEC, a newly described surgical approach which significantly extends survival. Novel therapeutics are needed in this recently described sarcoma.

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Compliance with Ethics Guidelines

Conflict of Interest Andrea Hayes-Jordan declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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