Intra-Abdominal Desmoplastic Small Round Cell Tumor: Current Treatment Options and Perspectives

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Intra-abdominal desmoplastic small round cell tumor (IDSRCT) is a rare and highly malignant soft tissue neoplasm, which is characterized by rapid progression and poor prognosis. The mechanism underlying the development of this neoplasm remains elusive, but all cases are characterized by the chromosomal translocation t (11;22) (p13; q12), which results in a formation of EWSR1-WT1 gene fusion. The diagnosis of IDSRCT is often made with core-needle tissue biopsy specimens or laparoscopy or laparotomy. Immunohistochemical analyses have shown the co-expression of epithelial, neuronal, myogenic, and mesenchymal differentiation markers. FISH or reverse transcription polymerase chain reaction detecting EWS-WT1 fusion can be performed to assist in molecular confirmation. There is no standard of care for patients with IDSRCT currently, and majority of newly diagnosed patients received the aggressive therapy, which includes >90% resection of surgical debulking, high-dose alkylator-based chemotherapy, and radiotherapy. More recently, targeted therapy has been increasingly administered to recurrent IDSRCT patients and has been associated with improved survival in clinical conditions. Immunotherapy as a possible therapeutic strategy is being explored in patients with IDSRCT. In this review, we summarize currently available knowledge regarding the epidemiology, potential mechanisms, clinical manifestations, diagnosis, treatment, and prognosis of IDSRCT to assist oncologists in comprehensively recognizing and accurately treating this malignancy.

Keywords: intra-abdominal desmoplastic small round cell tumor, EWS-WT1 gene, treatment, targeted therapy, immunotherapy

1. INTRODUCTION

Desmoplastic small round cell tumor (DSRCT), according to the International Classification of Disease for Oncology (2020), is categorized as a malignant tumor of uncertain differentiation. DSRCT typically occurs in the abdominal cavity, which is known as intra-abdominal desmoplastic small round cell tumor (IDSRCT) (1). Other primary sites have been reported (Figure 1). It is a rare and aggressive malignant soft tissue sarcoma that predominantly occurs in young male adults (20). IDSRCTs are associated with chromosomal translocation t (11;22) (p13; q12), which results in a formation of EWSR1-WT1 gene fusion (21, 22). IDSRCT mainly originates in the abdominopelvic cavity, involving...
the mesentery and retroperitoneum (23, 24). There is a lack of international consensus regarding the treatment of IDSRCT, and therapeutic regimens were derived from Ewing sarcoma’s (ES) treatment because of the involvement of the EWS gene and activation of similar oncogenic pathways in both ES and IDSRCT. The prognosis of IDSRCT is poor, with a median 5-year survival rate of 15%–25% (25). Because of the rarity of this malignancy, very few studies have investigated it, and most of these studies are case reports. This review summarizes the current knowledge on the epidemiology, potential mechanisms, clinical manifestations, diagnosis, treatment, and prognosis of IDSRCT, highlighting the modalities of treatment.

2. METHODS

This review summarizes the available literature on IDSRCT. We used the terms “abdominal,” “desmoplastic small round cell tumor,” and “intra-abdominal desmoplastic small round cell tumor” in our literature search. Previous reviews, articles, clinical trials, and case reports were included, and our search was not limited by language. Studies published from 1989 to 2021 were analyzed in the current review.

3. EPIDEMIOLOGY

IDSRCT is a rare and aggressive soft-tissue sarcoma. Its morbidity ranges between 0.2 and 0.74 cases per million people per year (26–28). IDSRCT mainly affects adolescents or young adults (median age at diagnosis: 27.0 years; range: 16–45 years), with a marked predominance in males (4:1 male-to-female ratio) (29, 30). No specific risk factors associated with the occurrence or progression of IDSRCT have been reported.

4. MECHANISM

The pathogenesis of IDSRCT remains elusive. However, it is uniquely characterized by chromosomal translocation t (11;22) (p13; q12), which results in the fusion of the EWS and WT1 genes. The wild-type WT1 gene encodes a zinc finger-containing protein, which acts as a repressor of transcription. With the fusion of the EWS and WT1 genes, the normal function of the zinc finger region of the WT1 gene is lost, leading to the transcriptional activation of at least 35 downstream target genes (31, 32). These target genes encode growth factors and growth factor receptors, such as platelet-derived growth factor (PDGF)-α, Type-1 insulin-like growth factor receptor (IGF-1-R), and epidermal growth factor receptor (EGFR) (33), which are related to tissue differentiation and the proliferation, adhesion, and metastasis of the tumor cells (34).

Recent genomics analysis of mutational profiles indicated that epithelial–mesenchymal transition (EMT), immune response, and the DNA damage response (DDR) are associated with gene deregulation in DSRCT (35). Whole-exome sequencing of six consecutive pre-treated DSRCT samples identified 137 unique somatic mutations: 133 mutated genes were case-
specific, and only 2 genes were overlapping among two cases but in different locations, which reveals the heterogeneity of the DSRCT genome. They also discovered that 27% of the 135 mutated genes are associated with DDR and EMT/mesenchymal–epithelial reverse transition (MER/T), which could result in tumor extreme heterogeneity followed by genomic instability, and consequently produce drug resistance (35). MER/T/EMT plays a crucial role in the metastasis and associated invasiveness of the sarcoma (36). Jiang et al. reported two novel somatic mutations, one associated with c-Met tyrosine kinase and the other related to PIK3CA gene, in 10 advanced stage DSRCT patients (37). The latter mutation was involved in the activation of the PI3K/AKT/MTOR pathway, facilitating the growth and proliferation of tumor cells (38).

5. CLINICAL MANIFESTATIONS

IDSRCT is commonly diagnosed at an advanced stage. Enlarged lymph nodes were seen in 50% of the patients, and distant metastasis was reported in 25% of the cases at the time of diagnosis (39). Widespread tumor nodules were also observed throughout the peritoneum, especially in the mesentery or omentum (40) (Table 1). The most common extraperitoneal metastasis is liver, followed by lymph node, bones, and lung (27, 28). The manifestations of IDSRCT are nonspecific and are related to the size, location, and speed of disease progression (40, 70, 71). It usually presents as a palpable abdominal mass with pain and other diverse symptoms, including distention, ascites, loss of weight, jaundice, fatigue, and constipation (Figure 2). Huge tumor masses can also cause compression symptoms, like intestinal obstruction and ureteral obstruction (72).

6. DIAGNOSIS

The diagnosis of DSRCT is often made with core-needle tissue biopsy specimens or laparoscopy or laparotomy (73). DSRCT is thought to originate from progenitor cells with polyphenotypic potential (38). Macroscopically, DSRCT is visible as a pale and firm mass in the peritoneal cavity with or without hemorrhage, necrosis, and cystic degeneration (20). Microscopically, histological examination shows uniform small round tumor cells grouped as clumps and nests with unclear cell borders, hyperchromatic nuclei, and inconspicuous nucleoli surrounded by hypocellular desmoplastic stroma. Glandular or rosette patterns or nuclear molding can be discovered. In addition, mitosis and apoptosis are common (71, 74, 75). However, a recent case report described a 12-year-old boy of DSRCT characterized by spindle cells with scant cytoplasm and with no desmoplastic stromal reaction, which reveals the heterogeneity of morphologic features in DSRCT (72). Immunohistochemical analyses of DSRCT have shown the co-expression of epithelial (cytokeratin and epithelial membrane antigen), neuronal (NSE and CD56), myogenic (desmin), and mesenchymal (vimentin) differentiation markers and WT1 (C-terminus antibody) (Table 2). Notably, >90% of patients with DSRCT express desmin and EMA (80). Most DSRCT patients typically do not express CD 99, HMB-45, S-100, and myogenin (75, 81).

As for molecular characteristics of DSRCT, previous literature described that almost all DSRCTs exhibit nuclear positivity for the DNA binding domain (C-terminal portion) of WT1, which can distinguish DSRCT from Wilms tumor and Ewing sarcoma (80). The specific chromosomal translocation t(11;22) (p13;q12) of DSRCT produces a chimeric EWSR1-WT1 fusion gene that encodes an aberrant transcription regulatory factor consisting of the C-terminal portion of WT1 and the trans-activation domain (N-terminal portion) of EWS (72). The EWSR1-WT1 fusion gene generally consists of exon 7 of the EWSR1 gene on chromosome 22 and exons 8–10 of the WT1 gene on chromosome 11 (82). However, several studies reported various alternative breakpoints for the t (11;22) (p13; q12) translocation (72, 83–85). Those fusion gene variants generally contain additional exons from EWS with conservation of the WT1 complement (EWS-WT1 8/8, 9/8, 10/8, and 9/7). Due to the heterogeneity of immunohistochemical findings, molecular methods are essential to verify diagnosis of DSRCT (86). Molecular analysis by fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction to detect EWSR1 rearrangement and the EWSR1-WT1 fusion gene, respectively, has also been used to confirm DSRCT diagnosis along with clinical findings (86). The molecular methods have higher sensitivity than that of immunohistochemical tools (87).

No specific tumor markers have been identified for the diagnosis of DSRCT, except elevated serum CA125 and NSE levels in some patients (3, 57, 71). For imaging information, ultrasound usually shows lobulated peritoneal masses with variable echogenicity, and dystrophic intratumoral calcification is discovered in 20% of cases (75). Computed tomography (CT) is considered as a primary auxiliary method for the assessment of response and follow-up of DSRCT, which typically show multifocal masses originating from the retroperitoneum or abdominopelvic cavity with poorly defined boundaries and unevenly enhanced signals. Cystic changes in large masses with heterogeneous enhancement can be found after contrast. Some cases had evidence of punctate calcification in primary mass (34, 88, 89). Twenty percent of IDRT patients show ascites, and lymph node involvement can be seen in 50% of cases (75). Magnetic resonance imaging (MRI) can detect potential lesions that are not observed by CT alone. Due to the presence of necrosis, hemorrhage, and fibrous stroma in DSRCT, it often shows heterogeneous high-intensity signals on T2-weighted images and hypointense or isointense signals on T1-weighted images in MRI with heterogeneous enhancement after gadolinium (74, 75). Although CT and MRI can help to identify primary sites of DSRCT, they have limited power to show the metabolic activity of tumors, which promotes the application of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and CT (FDG PET/CT) in DSRCT (90). A retrospective study indicated that FDG-PET may earlier predict histologic response to chemotherapy than macroscopic size change detected by CT. Although most patients
obtain rapid symptom relief when treated with chemotherapy, the change of tumor size is generally minimal because of the presence of abundant stromal component in IDSRCT, while the great decrease of metabolic activity can be detected by FDG-PET earlier (91). Furthermore, the specificity of FDG PET/CT is as high as 97.4% in DSRCT lesions, especially for involved lymph node and bone metastatic lesions, allowing early discovery of recurrent IDRCT and change of treatment strategy (90, 92, 93). Thus, FDG PET-CT should be considered as the preferred imaging method for monitoring patients with IDSRCT (90).

### 7. STAGING

There is no definite staging system for IDSRCT. Green et al. (94) proposed a staging system based on primary tumor burden, liver metastasis, and extra-abdominal metastasis. Primary tumor burden was measured using the peritoneal cancer index (PCI) score, calculated by measuring the tumor diameter in 13 abdominopelvic regions (95). In this staging system, a lower PCI score (<12) without liver or extra-abdominal metastasis was defined as Stage I; a higher PCI score (≥12) without liver or bone metastases, and a PCI score of 12 without liver or extra-abdominal metastases, was defined as Stage II. This system allows for a more accurate classification of IDSRCT patients and guides the selection of appropriate treatment strategies.

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**TABLE 1 | Published case reports and case series regarding IDSRCT.**

| Reference | Patient | Diagnosis | Metastases | Treatment | Regimen | Response | PFS (m) | OS (m) |
|-----------|---------|-----------|------------|-----------|---------|----------|---------|--------|
| (41)      | F/46    | Resection biopsy | Omentum | C+S     | HD-CAV  | SD       | 1       | NR     |
| (42)      | M/10    | Resection biopsy | Liver, lung | C+R     | VI      | PR       | 46      | 50     |
| (43)      | M/9     | Resection biopsy | NR | S+C     | VAI     | NR       | 7       | NR     |
| (44)      | F/23    | Biopsy | Liver lymph nodes | C    | VDC     | PD       | NR     | 4      |
| (45)      | M/26    | Biopsy | Pelvic | C+S+H+R | VDC/IE  | CR       | 48      | NR     |
| (46)      | M/18    | Fine-needle aspiration | NR | C+S+T   | Trabectedin | PR       | 8       | 48     |
| (47)      | M/14    | Biopsy | Liver, spleen, kidney, pancreas | C+S+R   | VDC/IE  | SD       | NR     | NR     |
| (48)      | M/27    | Biopsy | Spleen, lymph node | C+S   | VDC/IE  | Improved | NR     | NR     |
| (49)      | M/24    | Resection biopsy | Lymph node, omentum | C+S   | IMAP    | Death    | 0       | NR     |
| (50)      | M/21    | Biopsy | Liver, ileum, cecum | C+S   | VDC/IE  | SD       | 12      | NR     |
| (51)      | M/39    | Biopsy | Lymph node | C+S   | VDC/IE  | SD       | NR     | NR     |
| (52)      | M/16    | NR | Prostate, rectum | C+S+R | VNR–CTX | PR       | 17      | NR     |
| (53)      | M/26    | Biopsy | Liver, lymph node | C    | VNR–CTX | PR       | 4       | NR     |
| (54)      | M/NR    | NR | Bone, lymph nodes, liver | T    | Sunitinib | SD      | 10      | NR     |
| (55)      | M/NR    | NR | Lymph nodes, peritoneum | T    | Sunitinib | SD       | 4       | NR     |
| (56)      | M/NR    | NR | Peritoneum, lymph node | T    | Sunitinib | SD       | 6       | NR     |
| (57)      | M/NR    | NR | Liver, peritoneum | T    | Sunitinib | PD       | 1       | NR     |
| (58)      | M/NR    | NR | Liver, pleura, peritoneum | T    | Sunitinib | PD       | 1       | NR     |
| (59)      | M/NR    | NR | Liver, lung, peritoneum | T    | Sunitinib | PD       | 2       | NR     |
| (60)      | M/NR    | NR | Liver, peritoneum | T    | Sunitinib | PR       | 10      | NR     |
| (61)      | M/NR    | NR | Peritoneum, lymph node | T    | Sunitinib | PR       | NR     | NR     |
| (62)      | M/23    | Biopsy | Liver, peritoneum | C+S   | VDC/IE+Trabectedin | SD       | NR     | 24     |
| (63)      | M/19    | NR | Liver, pleura, peritoneum | C    | VDC/IE+Trabectedin | SD       | NR     | 16     |
| (64)      | F/30    | Resection biopsy | No | S    | No      | SD       | 6       | NR     |
| (65)      | M/31    | Resection biopsy | Brain, liver, lymph nodes | S+C+R | VDC/IE  | PD       | NR     | 17     |
| (66)      | M/27    | Tissue biopsy | Mesentry, peritoneum. | C    | PAVEP   | PR       | 12      |       |
| (67)      | F/22    | Frozen biopsy | NR | C    | 1.VDC2.VAC | PD       | NR     | 9      |
| (68)      | M/18    | Percutaneous biopsy | Mesentry, liver | C    | VDC/IE+irinotecan | PR       | 20      |       |
| (69)      | NR/NR   | NR | NO | C+T    | Pazopanib+ sirolimus | SD       | NR     | NR     |
| (70)      | F/11    | Resection biopsy | Ovary | S+C   | VDC/IE  | PD       | NR     | 11     |
| (71)      | F/7     | Resection biopsy | NO | S+C    | VDIE+VP-16 | SD       | NR     | NR     |
| (72)      | M/38    | Biopsy | Vessels, colon lymph nodes | S+R+C | CAP     | CR       | 30      | NR     |
| (73)      | F/30    | Frozen biopsy | Ovary, lung, lymph node | S+C   | VDC     | PR       | NR     | NR     |
| (74)      | M/52    | Biopsy | Omentum | C    | VDC/IE  | Death    | NR     | NR     |
| (75)      | M/16    | Biopsy | Colon, stomach, spleen | S    | NO      | SD       | NR     | NR     |
| (76)      | M/11    | Biopsy | NR | C    | ICE     | SD       | NR     | NR     |
| (77)      | M/11    | Biopsy | NR | C+S    | VAC/IVA  | PR       | NR     | NR     |
| (78)      | M/7     | Resection biopsy | Omentum, bowel, pelvis | S+C   | IRS-38  | SD       | 18      | NR     |
| (79)      | F/13    | Biopsy | Small bowel | C+S+ICT | IRS-38  | NR       | 9       | 11     |
| (80)      | M/11.5  | Resection biopsy | Liver, bladder, colon | S+C   | G-FLIP  | NR       | 8       | NR     |
| (81)      | F/26    | Biopsy | Pancreas, vein, duodenum | C    | VDC/IE  | SD       | NR     | 9      |
| (82)      | M/22    | Resection biopsy | Liver, peritoneum | C    | DC      | PR       | NR     | 13     |
| (83)      | M/29    | Resection biopsy | Small bowel, lymph node | S+C+R | VDC/IE  | Improved | NR     | NR     |

IDSRCT, intra-abdominal desmoplastic small round cell tumor; C, chemotherapy; S, surgery; R, radiotherapy; T, target therapy; H, HIPEC; SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease; M, male; F, female; EVAIA, etoposide, vincristine, doxorubicin, ifosfamide, and dactinomycin; VAC/IE, vincristine, actinomycin D, and cyclophosphamide, then alternated with ifosfamide and etoposide; IMAP, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide; VAI, ifosfamide, doxorubicin, vincristine; VDC, vincristine, doxorubicin, cyclophosphamide; PAVEP, cyclophosphamide, etoposide, doxorubicin, cisplatin; VI, irinotecan, vincristine; IT, irinotecan, temozolomide; PC, carboplatin, paclitaxel; DC, doxorubicin, cisplatin; VDIE, vincristine, doxorubicin, etoposide, ifosfamide; CAP, cyclophosphamide, doxorubicin, cisplatin; ICE, IFM, etoposide, carboplatin; IVA, actinomycin-D, vinristine, ifosfamide; IRS-38, oncovin, platinol, adriamycin, cyclophosphamide; G-FLIP, Gemzar, 5-FU/leucovorin, camptothecin, platinol; SCT, blood stem cell transplantation; NR, not reported.
extra-abdominal metastasis was defined as Stage II; liver metastasis without extra-abdominal metastasis was defined as Stage III; and extra-abdominal metastasis regardless of PCI score was defined as Stage IV (Table 3). However, this staging system requires further validation before being applied to all DSRCT types.

8. TREATMENTS

The therapeutic regimen for DSRCT is mainly derived from ES treatment because of the similarity in the oncogenic pathways involved and EWS gene fusion in both malignancies (31). Although multimodal treatments have been proposed for DSRCT patients, the prognosis remains poor (96). With the widespread utilization of targeted therapy, the prognosis of DSRCT patients has markedly improved. Published case reports and case series of treatments administered to DSRCT patients are summarized in Table 1.

8.1. Surgery

Radical surgical excision without residual disease is usually impossible because of the presence of multiple serosal tumor nodules and obscure boundary of DSRCT (97). Thus, cytoreductive surgery (CRS) is regarded as the fundamental therapy for DSRCT patients, which is defined as the resection

TABLE 2 | The features of immunohistochemical staining of DSRCT reviewed from published case reports and case series.

| Vimentin | Desmin | EMA | CK | WT-1 | CD99 | Myogenin | S100 | NSE | Leu-7 |
|----------|--------|-----|----|------|------|----------|------|-----|-------|
| Shen et al. (46) | NR | + | NR | + | + | – | – | – | NR | NR |
| Shi et al. (78) | + | + | + | + | + | NR | – | + | NR |
| Ambar et al. (42) | NR | + | + | + | – | NR | NR | NR | NR |
| Li et al. (24) | NR | + | + | + | – | NR | NR | – | – | NR |
| Reisner et al. (48) | NR | + | NR | + | NR | NR | NR | NR | NR |
| Briseño-Hernández et al. (49) | NR | + | NR | NR | NR | NR | NR | NR | NR |
| Kandhari et al. (50) | + | + | NR | + | NR | NR | NR | NR | NR |
| Nathan et al. (51) | NR | + | + | NR | NR | + | NR | NR | NR |
| Frezza et al. (54) | NR | + | NR | NR | NR | NR | NR | NR | NR |
| Frezza et al. (110) | NR | + | NR | NR | NR | NR | NR | NR | NR |
| Saleh et al. (4) | NR | NR | + | NR | NR | + | – | NR | NR |
| Huang et al. (5) | + | + | NR | + | + | NR | NR | NR | NR |
| Ordi (77) | + | + | + | NR | + | NR | NR | + | NR |
| Takahira et al. (56) | + | + | NR | + | NR | NR | NR | + | NR |
| Wakahashi et al. (57) | + | + | NR | – | NR | NR | NR | – | NR |
| Hirano et al. (58) | + | + | NR | NR | NR | NR | NR | NR | NR |
| Slomovitz et al. (60) | NR | + | + | NR | – | NR | NR | NR | NR |
| Eaton et al. (61) | NR | + | NR | – | NR | NR | NR | NR | NR |
| Zhang et al. (62) | NR | + | + | NR | NR | – | NR | NR | NR |
| Ferreira et al. (44) | NR | + | + | NR | NR | – | NR | NR | NR |
| Shimazaki (78) | NR | + | + | NR | NR | – | – | NR | NR |
| Kim et al. (67) | + | – | NR | – | NR | NR | NR | NR | NR |
| Devaney (79) | + | + | + | NR | NR | – | NR | NR | NR |
| Ujihara et al. (66) | NR | + | NR | – | NR | NR | NR | NR | NR |
| Takekawa et al. (65) | + | + | NR | NR | NR | NR | NR | NR | NR |
| Baz et al. (64) | + | + | NR | NR | NR | NR | NR | NR | NR |
| Xie et al. (63) | + | + | NR | NR | NR | NR | NR | NR | NR |

DSRCT, intra-abdominal desmoplastic small round cell tumor; +, positive; -, negative; +/-, suspicious positive; NR, not reported; EMA, epithelial membrane antigen; CK, cytokeratin; NSE, neuron-specific enolase.
of ≥90% of the tumor burden, preserving the non-invaded peritoneum macroscopically (70, 98). The lesions are generally confined to the serosal or superficial muscle layers, although there is dissemination throughout the peritoneal cavity, allowing the treatment of local tangential resection (99). The surgical resection extension is usually extensive, including the resection of primary disease with acceptable margins, peritonectomy, lymphadenectomy, and the resection of involved adjacent tissue (89). To preserve bowel length, wedge excision can be performed to remove masses that invade deeply into the bowel (99). According to the recent studies, patients treated with complete CRS have significantly improved survival compared with patients receiving insufficient or no surgery with macroscopic residual tumor (the 3-year survival rates 49.6% vs. 31.1% vs. 13.7%, p = 0.009) (70, 100). Complete resection of metastases combined with cytoreduction is essential in patients with extra-abdominal disease, while locoregional surgery alone typically cannot be considered if patients have extra-abdominal lesion. Moreover, it is not a first option for IDSRCT patients with extensive subdiaphragmatic lesion or unresectable periportal lesion. Moreover, it is not a typically cannot be considered if patients have extra-abdominal disease, while locoregional surgery alone typically cannot be considered if patients have extra-abdominal lesion. Therefore, extensive surgical resection-associated complications should be considered before the administration of surgery.

8.2. Chemotherapy

IDSRCT is sensitive to chemotherapy; therefore, neoadjuvant chemotherapy is usually recommended for patients with advanced-stage and unresectable IDSRCT (27). Several studies have suggested that IDSRCT patients who have evident efficacy to neoadjuvant chemotherapy have an improved overall survival (OS) than those who are resistant to neoadjuvant therapy (27, 103). However, IDSRCT treated with neoadjuvant chemotherapy may not have a significant reduction of size because of its large stromal component, which should not delay or prevent an attempt of administration of CRS (91). The chemotherapy regimen of IDSRCT mainly follows the same schedule as that used in ES (25). The P6 chemotherapy regimen, comprising vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide (VDC/IE), is the most common neoadjuvant chemotherapy regimen for IDSRCT patients (43, 69). Vincristine, doxorubicin, and ifosfamide are a reasonable alternative regimen for older people who may not tolerate the intense regimen (73). For P6 chemotherapy-resistant patients, temozolomide/irinotecan, cyclophosphamide/topotecan, gemcitabine/docetaxel, and high-dose ifosfamide can be considered as second- or third-line chemotherapy regimens (Table 4) (75, 80, 104). Some IDSRCT patients receive adjuvant chemotherapy (high-dose 5-FU, temozolomide/irinotecan-based therapy, and high-dose ifosfamide) (104–106) in combination with radiotherapy after CRS to increase the effectiveness of the surgery (105, 106). Palliative chemotherapy is administered to patients with metastatic tumors at the time of diagnosis (27). Several regimens, such as irinotecan in combination with vincristine (42), vinorelbine plus low-dose cyclophosphamide (52), and trabectedin (45, 54), have been reported to show clinical benefits for refractory IDSRCT patients. Specifically, trabectedin has been shown to interact with the minor groove of DNA, affecting several transcription

### Table 3 | DSRCT staging criteria proposed by Hayes-Jordan, Green et al.

| Stage | Primary tumor (PCI) | Liver metastasis | Extra-abdominal metastasis |
|-------|-------------------|-----------------|---------------------------|
| I     | <12               | No              | No                        |
| II    | ≥12               | No              | No                        |
| III   | Any               | Yes             | No                        |
| IV    | Any               | Yes or no       | Yes                       |

DSRCT, desmoplastic small round cell tumor; PCI, peritoneal cancer index.

### Table 4 | The common chemotherapeutic regimens for the treatment of DSRCT.

| Regimen | Agent | Dose |
|---------|-------|------|
| First-line |       |      |
| VDC/IE  | Vincristine | 1.5 mg/m² |
|         | Doxorubicin | 37.5 mg/m² |
|         | Cyclophosphamide | 1,200 mg/m² |
|         | Etoposide | 100 mg/m² |
|         | Ifosfamide | 1,800 mg/m² |
| VDI     | Vincristine | 1.5 mg/m² |
|         | Doxorubicin | 37.5 mg/m² |
|         | Ifosfamide | 1,800 mg/m² |
| VDIE    | Vincristine | 1.5 mg/m² |
| PAVEP   | Doxorubicin | 20 mg/m² |
|         | Ifosfamide | 3,000 mg/m² |
|         | Etoposide | 150 mg/m² |
|         | Cyclophosphamide | 300 mg/m² |
|         | Etoposide | 75 mg/m² |
|         | Doxorubicin | 40 mg/m² |
|         | Cisplatin | 100 mg/m² |
| Second-line |       |      |
| Temozolomide/irinotecan | NR |
| Cyclophosphamide/topotecan | NR |
| GD      | Gemcitabine | 1,000 mg/m² |
|         | Docetaxel | 100 mg/m² |
|         | High-dose ifosfamide | NR |
| VIP     | Etoposide | NR |
|         | Ifosfamide | NR |
|         | Cisplatin | NR |
| HIPEC   | Cisplatin | 100 mg/m² |
|         | Oxaliplatin | 300–460 mg/m² |
| MC      | Mitomycin | 75 mg/m² |
|         | Cisplatin | 120 mg |

DSRCT, desmoplastic small round cell tumor; NR, not reported.
factors, DNA repair molecules, and DNA-binding proteins; perturbing the cell cycle; and subsequently causing the death of cancer cells (107). Trabectedin has been deemed safe and effective in pre-treated IDSRCT patients who were refractory to conventional chemotherapy and resection (45, 54).

Other special chemotherapy forms, such as hyperthermic intraperitoneal chemotherapy (HIPEC), are also considered in patients with extensive metastasis over the abdominal cavity (70). However, the role of HIPEC remains controversial. A previous retrospective study has reported a significant improvement in the 3-year OS of patients treated with surgery and HIPEC (94), and other studies have shown that CRS followed by HIPEC may improve the disease control rate (DCR) in patients with peritoneal surface metastasis (106). Conversely, some studies have suggested that HIPEC is not associated with a better outcome (27, 70). Few patients who received CRS and HIPEC have been reported to need long-term parenteral nutrition or surgical intervention due to severe side effects, such as hemorrhagic cystitis, adhesive bowel obstruction, and sclerosing peritonitis (108). Therefore, assessing the actual effectiveness of HIPEC requires further studies.

8.3. Radiotherapy

Because of the multicentric growth tendency in the abdominopelvic cavity of IDRCT, whole-abdominopelvic radiotherapy (WAP RT) is a more effective treatment than locoregional radiotherapy (93). WAP RT is occasionally used as a consolidative therapy after CRS to remove microscopic or minimal residual disease (<2 cm) (88, 99). Treatment is performed with megavoltage photon beams by AP/PA fields into the entire peritoneal cavity. The median dose for patients without residual disease is 30 Gy in 1.5–1.5 Gy fractions, while for patients with residual lesions, the dose can be increased to 45–50 Gy (70, 99). IDSRCT patients treated with WAP RT combined with CRS and chemotherapy experienced prolonged survival (104). As for complications, gastrointestinal and hematological toxicities were the most common reported acute complications, while small bowel obstruction was the most common late toxicity in IDSRCT patients who underwent WAP RT (109). Acute complications can be treated with supportive care or symptomatic treatment, while surgical intervention is required in up to 10% of small bowel obstruction (106). Patients subjected to intensity-modulated radiation therapy (IMRT) reported a lower incidence of hematological toxicities compared to those who underwent WAP-RT (109). IMRT was found to selectively decrease the irradiated doses of adjacent normal organs (e.g., liver, kidneys, and pelvis), allowing even dose distribution to the peritoneal surfaces (106). Furthermore, there is no significant difference in OS between patients treated with IMRT and WART (109). In addition to being used as an adjunctive treatment, radiation can also be administered as a palliative treatment for recurrent IDSRCT (104).

8.4. Targeted Therapy

The formation of EWSR1-WT1 fusion gene can activate downstream signaling pathways, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin growth factor (IGF)-1. Those pathways may be potential targets for treatment of IDSRCT (38). Until now, targeted therapy has shown its clinical benefit in IDSRCT patients who had tumor relapse or progression despite first-line or second-line treatment (38). Based on previous studies, tyrosine kinase inhibitors (TKI), including pazopanib (110), sunitinib (53), sorafenib (23), anlotinib (104), apatinib (76), imatinib (111), anti-VEGFR monoclonal antibody (e.g., bevacizumab) (68), IGF-1-R inhibitors (112, 113), mTOR inhibitors (114), and PARP inhibitors (100) were used for the therapies and were found to be effective in select IDSRCT cases. Targeted therapy-treated patients who were reviewed from case reports/series and our hospital are listed in Table 5. All ongoing clinical trials are summarized in Table 6.

8.4.1. Pazopanib

Pazopanib, a TKI, targets the stem cell factor receptor c-Kit, PDGFR-α and -β, and VEGFR-1, 2, and 3 to prohibit angiogenesis and tumor proliferation (117). Pazopanib has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of patients with renal cell carcinoma (RCC) and sarcoma (118). IDSRCT overexpresses VEGF-A, VEGF-R, and PDGF, which gives rationality to the administration of pazopanib in pretreated IDSRCT patients (119, 120). Pazopanib has been demonstrated to achieve a variable DCR of 61% and 78% for patients who received prior chemotherapy and those who did not, respectively. Median progression-free survival (PFS) of 9.2 months and OS of 15.4 months have also been observed with pazopanib treatment. The common adverse reactions following this treatment were neutropenia, hypertension, fatigue, and diarrhea (110, 121).

8.4.2. Sunitinib

Sunitinib has a mechanism of action like that of pazopanib, and it targets PDGFR, VEGFR, c-KIT, RET, colony-stimulating factor 1, and Flt3 (122). The FDA has approved sunitinib for the management of imatinib-refractory gastrointestinal stromal tumors (GISTs), RCC, and pancreatic neuroendocrine tumor (123). This agent has also shown clinical effectiveness in pretreated IDSRCT patients. In a case series comprising eight patients, six pretreated IDSRCT patients achieved an improved clinical outcome (partial remission [PR] and stable disease [SD]) after sunitinib treatment, and no severe adverse response was reported (53).

8.4.3. Sorafenib

Sorafenib, a multitargeted TKI, targets c-KIT, PDGFR-β, VEGFRs 2–3, and Flt-3. Sorafenib has been approved for treating hepatocellular carcinoma, RCC, and thyroid cancer (124). In a retrospective study, two progressive IDSRCT patients received sorafenib and progressed at 4 months. Of the two patients, one developed skin toxicity, while the other had to terminate the treatment due to severe abdominal pain (grade = 3) (23). The true efficacy of sorafenib treatment for DSRCT patients requires large sample data to further validate the results.
| Reference | Patient | 1-line therapy | 2-line therapy | 3-line therapy | 4-line therapy | 5-line therapy | 6-line therapy | Response | T-PFS (m) | OS (m) |
|-----------|---------|----------------|----------------|----------------|----------------|----------------|----------------|----------|-----------|-------|
| (115)     | 31/M    | Gemcitabine+ nedaplatin | Cyclophosphamide-epirubicin-vincristine | Apatinib | NA | NA | NA | NA | PR | NR | NR |
| (76)      | 32/M    | Apatinib | NA | NA | NA | NA | NA | NA | Improved | NR | NR |
| (68)      | 37/M    | PCB+ bevacizumab | NA | Sunitinib | NA | NA | NA | NR | 2 | NR |
| (23)      | NR      | MAID-ASCT | Gemcitabine-cisplatin | Carboplatin-etoposide | Sunitinib | NA | NA | NR | 5.5 | NR |
| (23)      | NR      | VAI-Adriamycin-cisplatin-etoposide-cyclophosphamide | Etoposide-carboplatin-busulfan-thiotepa | Temozolomide | Temozolomide-irinotecan | Bevacizumab | NA | Death | 2 | NR |
| (23)      | NR      | MIA | VAC | Ridaforolimus | Sunitinib | NA | NA | NR | 3 | 38 |
| (23)      | NR      | IVADO Bevacizumab | Navelbine-cyclophosphamide | Dalotuzumab | Sunitinib | NA | NA | NR | 3 | NR |
| (23)      | NR      | Adriamycin-ifosfamide-etoposide | Cyclophosphamide | Trabectedin | Sunitinib | NA | NA | NR | 2 | 19 |
| (23)      | NR      | MAI | VAC | FOLFIRI | Sorafenib | NA | NA | NR | 2 | NR |
| (23)      | NR      | LV5Fu-Ciplatine | HIEPO-FOLFIRI | Al | Sorafenib | NA | NA | NR | 4 | NR |
| (23)      | NR      | MAI | Gemcitabine-docetaxel | Anlotinib | Apatinib | NA | NA | PR | >14 | >21 |
| Hospital 46/M | MAID | GD | Anlotinib | NA | NA | NA | SD | >6 | NO |
| Hospital 28/M | MAID | GD | Sunitinib | NA | NA | NA | NA | SD | >6 | NO |

**TABLE 5** | Retrospective cases from published reports and our hospital of IDSRCT patients treated with target therapy.

IDSRCT, intra-abdominal desmoplastic small round cell tumor; M, male; F, female; T, target therapy; PR, partial response; OS, overall survival; PFS, progression-free survival; ASCT, autologous stem cell transplantation; NR, not reported; NA, not available; PCB, carboplatin-paclitaxel; MIA, mesna-adriamycin-ifosfamide-dacarbazine; Sunitinib, autologous stem cell transplantation; HIPEC, hyperthermic intraperitoneal chemotherapy; FOLFIRI, 5 FU-oxaliplatin-irinotecan; MIA, mesna-adriamycin-ifosfamide; VAI, vincristine-actinomycin-etoposide; VAC, vincristine-actinomycin-D-cyclophosphamide; IVADO, ifosfamide-vincristine-actinomycin-D-doxorubicin; GD, gemcitabine plus docetaxel; AC, Adriamycin-cyclophosphamide; AI, Adriamycin-holoxan.

The bold values represent the targeted therapy during the treatment process.
8.4.4. Apatinib

Apatinib, a novel multitargeted TKI, inhibits the expression of VEGFR-2, RET, c-Kit, and c-Src tyrosine kinases, selectively targeting VEGFR-2 (125). Apatinib is used for treating several tumor types, including gastric neoplasm (126), non-small cell lung cancer (NSCLC) (127), and colorectal cancer (CRC) (128). A case report showed that the tumor-related symptoms of IDSRCT patients were reduced quickly after the initiation of apatinib treatment (76). In another case report, one patient with IDSRCT received systemic chemotherapy (cyclophosphamide, epirubicin, and vincristine) plus apatinib and achieved PR after two cycles of treatment (115). Apatinib may be an alternative strategy for patients with IDSRCT. In a previous study, we presented the case of a 46-year-old man with metastatic IDSRCT admitted to our hospital. Although he had failed the first-line (MAID: mesna, doxorubicin, ifosfamide, and dacarbazine) and second-line chemotherapies (GD: gemcitabine plus docetaxel), he showed positive response to apatinib and quickly reached PR and achieved more than 14 months of PFS. This patient needed to reduce the dose of apatinib because of grade 3 hypertension and grade 2 digestive tract reaction. These adverse reactions resolved rapidly after dose reduction and usage of hypotensors.

8.4.5. Anlotinib

Anlotinib mainly targets VEGFRs 1–3, PDGFR-α and -β, fibroblast growth factor receptors (FGFRs) 1–4, EGFR, c-Kit, Met, and stem cell factor receptors (104, 116). Anlotinib plays a crucial role in the treatment of NSCLC and thyroid cancer (129). A case report showed that one IDSRCT patient who progressed after resection and chemotherapy (ifosfamide and liposomal doxorubicin) received anlotinib as the second-line therapy, which reduced invasive lymph node size with a PFS of 4 months. Only fatigue (grade = 1) and high triglyceride levels (grade = 1) were observed as side effects (104). In a previous study, we presented the case of a 28-year-old man admitted to our hospital with multiple metastatic and unresectable IDSRCT lesions. He received anlotinib plus chemotherapy (VAD) as the first-line treatment and achieved an SD of over 6 months.

**TABLE 6 | Clinical trials of DSRCT patients.**

| ClinicalTrials.gov Identifier | Conditions | Status | Phase | Interventions | Comparison | Participants |
|-----------------------------|------------|--------|-------|---------------|------------|--------------|
| Chemotherapy                |            |        |       |               |            |              |
| NCT04096521                 | Relapsed/refractory DSRCT, rhabdomyosarcoma | Recruiting | I/II | Prexasertib + Irinotecan | Single-arm | 30           |
| NCT03275918                 | Relapsed/refractory sarcoma, including DSRCT | Active | II   | Nab-paclitaxel  | Single-arm | 60           |
| NCT00055992                 | Relapsed or refractory DSRCT, ES, PNET         | Completed | II   | Exatecan mesylate | Single-arm | NR           |
| Radiotherapy                |            |        |       |               |            |              |
| NCT01277744                 | DSRCT patients underwent surgery               | Completed | II   | HIPEC with cisplatin | Single-arm | 22           |
| Target therapy              |            |        |       |               |            |              |
| NCT01189643                 | Newly diagnosed DSRCT                          | Active | I    | Irinotecan + Temozolomide + Bevacizumab + High Dose Alkylator-Based Chemotherapy | Single-arm | 15           |
| NCT00417807                 | Refractory DSRCT                               | Completed | I/II | Imatinib mesylate | Single-arm | 9            |
| Target therapy + Chemotherapy|            |        |       |               |            |              |
| NCT00720174                 | Unresectable/metastatic soft tissue sarcoma, including DSRCT | Completed | I    | Oxatumumab and doxorubicin hydrochloride | Single-arm | 30           |
| NCT04145349                 | Refractory/refractory DSRCT                    | Recruiting | I/II | Ramucirumab + Cyclophosphamide + Vinorelbine | Cyclophosphamide + Vinorelbine | 34           |
| Immunotherapy               |            |        |       |               |            |              |
| NCT02982941                 | B7-H3-expressing relapsed/refractory solid tumors, including DSRCT | Completed | I    | Enoblituzumab | Single-arm | 25           |
| Radioimmunotherapy          |            |        |       |               |            |              |
| NCT01909644                 | Solid tumors Involving the peritoneum, including DSRCT | Active | I    | Radioimmunotherapy with 131I-H9 | Single-arm | 54           |
| Other therapy               |            |        |       |               |            |              |
| NCT04213794                 | Recurrent, refractory/recurrent abdominopelvic tumors, including DSRCT | Recruiting | I   | HIPEC with doxorubicin and cisplatin | Single-arm | 43           |
| NCT04350487                 | Recurrent/refractory solid tumors, including DSRCT | Recruiting | I   | ASCT after chemotherapy | Single-arm | 40           |

DSRCT, desmoplastic small round cell tumor; ES, Ewing’s sarcoma; PNET, primitive neuroectodermal tumor; WT, Wilms tumor; HIPEC, hyperthermic intraperitoneal chemotherapy; VDC/IE, vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide, CHPP, continuous hyperthermic peritoneal perfusion; ASCT, allogeneic stem cell transplantation.
8.4.6. Imatinib
Imatinib mesylate has been recommended as a treatment for GISTs and chronic myeloid leukemia (130). Notably, this agent also targets other tyrosine kinase receptors, such as PDGFR-R and c-KIT (111). PDGFR-A and PDGFR-β are related to tumor cell growth and proliferation (38) and are overexpressed in DSRCT (119). However, the efficacy of imatinib for DSRCT has been found to be limited. Eight patients who were refractory to conventional treatment were administered imatinib, and only one patient achieved SD, while seven patients progressed rapidly 3 months after the initiation of imatinib. The toxicities were tolerated, and no severe adverse events were observed (111). Similarly, a phase II study suggested that imatinib was not associated with clinical benefits in pediatric patients with refractory DSRCT (131).

8.4.7. Monoclonal Antibody Targeting VEGF
Bevacizumab is a monoclonal antibody that targets VEGF-A. It has been recommended for the treatment of metastatic CRC, advanced NSCLC, advanced cervical cancer, and metastatic RCC (132). A previous study has found that VEGFR-2 and VEGFA are overexpressed in DSRCT cell lines and xenograft models (31). One IDSRCT patient who underwent prior partial resection received bevacizumab and achieved an OS of 34 months (68). Notably, bevacizumab in combination with WART can be used to eradicate residual disease after surgery because it increases the sensitivity of the tumor nodules to radiotherapy (106). An ongoing clinical trial (NCT01189643) is exploring the combination of irinotecan, temozolomide, and bevacizumab in combination with chemotherapy, being assessed in a phase II clinical trial on DSRCT (Table 4; NCT04145349).

8.4.8. IGF1R Inhibitor
IGF1R inhibitors can inhibit the proliferation of tumor cells by blocking the binding between IGFIR and IGF-1 and 2 (133). In addition, these inhibitors exert anti-angiogenic effects by targeting VEGF (134). Common IGF1R inhibitors include ganitumab and cixutumumab. IGFIR inhibitors are used for treating ES (135). In a Phase II study, 25% of clinical benefit (DCR ≥ 6 months) was achieved in DSRCT patients treated with ganitumab. This study suggested that ganitumab could prolong the survival of DSRCT patients with a median PFS of 19.0 months. Notably, five patients had to undergo dose reductions due to thrombocytopenia (grade = 3) caused by ganitumab. Other grade 3 toxicities, including hyperglycemia, leukopenia, neutropenia, and grade 4 thrombocytopenia, were also reported (112). In another study, SD was observed in two-thirds of pretreated patients who received cixutumumab in combination with temsirolimus (an mTOR inhibitor) (113).

8.4.9. mTOR Inhibitor
The PI3K/Akt/mTOR pathway is constitutively activated in DSRCT progression, mainly through mTORC-2 expression (136), and it is related to cancer cell growth and survival in sarcoma (137). One IDSRCT patient, who resisted chemotherapy and anti-androgen therapy, maintained an SD of 10 months when treated with temsirolimus (114). Furthermore, mTOR inhibitor plus pazopanib led to an SD of 11 months in one IDSRCT patient who progressed after treatment with pazopanib alone (59). Nevertheless, mTOR inhibitor plus IGFIR inhibitor showed limited efficacy in DSRCT treatment (138).

8.4.10. PARP Inhibitors
The DDR network may be a potential target for DSRCT due to the recent discovery that 27% of mutated genes of DSRCT are related to DDR (35). Poly (ADP-ribose) polymerase 1 (PARP1) is a key enzyme for base excision repair of single-strand DNA breaks, participating the recruitment of DNA repair proteins (139). PARP inhibitor has been reported to be effective in sarcoma with deficiency in DDR (38). Anke E. M. van Erp and coworkers discovered that PARP1 expression was observed in 100% of clinically derived DSRCT tumor tissues (100). They also found that DSRCT cells have a high sensitivity profile to the PARP inhibitor olaparib, and the combination of olaparib with temozolomide (an alkylating agent) in JN-DSRCT-1 cells results in synergistic effects, inducing cell cycle arrest followed by cell apoptosis, consequently leading to tumor reduction in vitro and in vivo.

DSRCT patients who progress or relapse after first- and second-line treatment can first receive anti-VEGF monoclonal antibodies, like bevacizumab or TKI, that act on multiple pathways simultaneously (e.g., c-Kit, PDGFR-a and -b, and VEGFR-1, 2, and 3, Flt3, RET), including pazopanib, sunitinib, anlotinib, and apatinib. Among them, imatinib and sorafenib caused no benefit, which should not be considered in DSRCT patients. Subsequent lines of management include IGFIR inhibitor or mTOR inhibitor. Notably, the effect of PARP inhibitor needs to be further verified in clinical studies. The existing preclinical and clinical data suggest some effect of targeted therapy in DSRCT patients. However, the observed role predominantly is tumor stabilization rather than disease regression. Those potential targets are worthy of further exploration (23, 53, 68, 76, 100, 110–114).

8.5. Immunotherapy
Although immunotherapy has shown an unprecedented response in multiple tumor types, there is no clinical evidence of its efficacy in DSRCT. Some potential targets for immunotherapy have been detected in DSRCT. CD276, now called B7H3, and GD2 are detected in IDSRCT. CD276, now called B7H3, and GD2 are related to tumor cell growth and proliferation (38) and are overexpressed in DSRCT (119). However, the efficacy of imatinib for DSRCT has been found to be limited. Eight patients who were refractory to conventional treatment were administered imatinib, and only one patient achieved SD, while seven patients progressed rapidly 3 months after the initiation of imatinib. The toxicities were tolerated, and no severe adverse events were observed (111). Similarly, a phase II study suggested that imatinib was not associated with clinical benefits in pediatric patients with refractory DSRCT (131).

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with 131I-8H9 for patients with DSRCT (NCT01099644). The function of GD2 in DSRCT has not been adequately identified. However, some studies have indicated that GD2 might increase the adhesion between extracellular matrix proteins and tumor cells and contribute to the metastasis of the neoplasm (33). Notably, GD3, an upstream molecule in the biosynthesis of GD2, has also been found in 70.0% of DSRCT patients. We speculate that GD3 may be a potential target of immunotherapy in DSRCT patients (142). Immune checkpoint inhibitors targeting PD-1 and CTLA-4 have been demonstrated to prolong survival in several tumors, including NSCLC, RCC, and melanoma (143), but its clinical effect in DSRCT remains unknown. Pembrolizumab, an anti-PD-1 agent, is now being tested in patients with rare sarcoma (including 6 patients with DSRCT) in a phase 2 clinical trial (NCT03012620).

8.6. Androgen Blockade Agent
Bulbul et al. reported higher expression of androgen receptor in DSRCT patients than in those with ES (144). Hence, androgen blockade agents were tested in DSRCT patients, but its efficacy remains controversial. In a case report analyzing six patients treated with combined androgen blockade, 50% of the patients showed a positive response to the therapy (132), while in one patient, the tumor progressed after 2 months of treatment (114).

8.7. Autologous Stem Cell Transplant
ASCT has been performed in DSRCT patients (145). In a case report, a complete response (CR) was seen in DSRCT patients after resection, chemotherapy (VAC+VAP), and ASCT (146). Another study also found that ASCT could significantly improve OS in DSRCT patients who were in remission (147). Moreover, a retrospective study reported improved disease-free survival and OS in ASCT-treated DSRCT patients with residual tumors (148). Owing to the small sample size of the abovementioned studies, the true effectiveness of ASCT needs further validation in the future.

9. PALLIATIVE CARE AND COMPLICATIONS MANAGEMENT
Advanced DSRCT patients with extensive systemic metastases who cannot tolerate surgery or systemic chemotherapy may consider targeted therapy with mild adverse reactions, including TKI inhibitors, mTOR inhibitors, or bevacizumab (53, 59, 68, 121). Nutritional care is essential for patients with advanced tumors. Pharmacological agents and pharmaconutrients have limited effects in patients with advanced cancer. If possible, patients with advanced tumor should engage in regular physical activity and adopt a prudent diet (149). For patients with tumor mass-associated compression symptoms, like intestinal obstruction and ureteral obstruction, palliative surgery can be considered, but the benefits and risks of palliative surgery must be balanced with special consideration in patients with advanced DSRCT.

10. PROGNOSIS AND FOLLOW-UP
The prognosis of DSRCT is poor. Patients with DSRCT had a dismal survival with 3- and 5-year survival rates from 44% to 15%-25% and a median OS of 1725 months (70, 75). Patients with hepatic/portal metastasis (150), resistance to neoadjuvant chemotherapy (27), and CD99 staining positive expression (100) have worse prognosis. Furthermore, local solitary lesions, no metastases, complete CRS, and adjuvant chemotherapy were independent risk factors for OS of DSRCT (151). Some studies argued that some factors, such as sex, age, postoperative complications, lymph node metastases, the presence of extra-abdominal lesions at initial presentation, and tumor size (1, 29, 102), have no significant effect on the survival of DSRCT. Despite the implementation of multimodal therapy, most DSRCT patients experience quick relapses with a median PFS of 10–14 months (27, 75). Therefore, close follow-up is necessary after completion of treatment. If possible, PET-CT scan every 3 to 6 months is required, which can detect the change of metabolic activity prior to macroscopic neoplasm growth (90).

11. FUTURE PERSPECTIVES
CRS combined with VDC/IE chemotherapy regimen and WAP-RT are regarded as the standard treatments for DSRCT. Other therapies, such as molecularly targeted treatments, ASCT, and androgen blockade agents, can be considered when tumor progresses or relapses after standard therapy. Despite multimodal treatments, DSRCT still has a dismal clinical outcome. The targeted agents for optimal effectiveness for DSRCT remain unclear. Further research should be directed at exploring the potential effect of various targeted therapies in these patients with DSRCT. Several potential targets like the DDR or MErT/EMT are waiting further exploration. Furthermore, immunotherapy as a possible therapeutic choice has limited extent effect in preclinical studies, which should be further verified in clinical conditions in the future.

12. CONCLUSION
DSRCT refers to a rare and aggressive soft tissue malignancy that predominantly occurs in a young male population. It is often diagnosed with extensive peritoneal metastasis and has a dismal prognosis. Immunohistochemical analyses of DSRCT are characterized by co-expression of epithelial, neuronal, and mesenchymal differentiation markers. FISH or reverse transcription polymerase chain reaction detecting EWS-WT1 fusion can be performed to assist in molecular confirmation. Multimodal treatments, including surgery, chemotherapy, and radiotherapy, in patients with DSRCT have achieved improved outcome. Currently, targeted therapy and immunotherapy have expanded the treatment options for DSRCT patients and are
associated with improved survival rates in preclinical or clinical studies. Hepatic/portal metastasis and effect of neoadjuvant chemotherapy, number of lesions, and surgery types are associated with prognosis of IDSRCT. Due to the rarity and poor prognosis of this neoplasm, further studies are required to propose effective regimens for IDSRCT patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

GW reviewed the literature, and wrote the manuscript. XS wrote and revised the manuscript. YZ rechecked the manuscript. XL and XC assisted in drawing. MQ designed and revised the manuscript.

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