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Can we cure patients with abdominal Desmoplastic Small Round Cell Tumor? Results of a retrospective multicentric study on 100 patients

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ABSTRACT

Background: Despite being associated with a very poor prognosis, long-term survivors across all series of Desmoplastic Small Round Cell Tumor (DSRCT) have been reported.
Aim of the study: To analyze patients 'characteristics associated with a prolonged survival after DSRCT diagnosis.
Methods: All consecutive patients treated for DSRCT in nine French expert centers between 1991 and 2018 were retrospectively analyzed. Patients with a follow-up of less than 2 years were excluded and cure defined as being disease-free at least 5 years.
Results: 100 pts were identified (median age 25 years, 89% male). 27 had distant metastases at diagnosis and 80 pts underwent upfront chemotherapy (CT). 71 pts were operated, 20 pts without prior CT). Surgery was macroscopically complete (CC0/1) in 50 pts. Hyperthermic intraperitoneal Chemotherapy (HIPEC) was administered during surgery in 15 pts 54 pts had postoperative CT and 26 pts had postoperative whole abdomino-pelvic RT (WAP-RT). After a median follow-up of 103 months (range 23–311), the median overall survival (OS) was 25 months. The 1- year, 3-year and 5-year OS rates were 90%, 35% and 4% respectively. 5 patients were considered cured after a median disease-free interval of 100 months (range 22–139). Predictive factors of cure were female sex (HR = 0.49, p = 0.014), median PCI < 12 (HR = 0.32, p = 0.0004), MD Anderson stage I (HR = 0.25, p < 0.0001), CC0/1 (HR = 0.34, p < 0.0001), and WAP-RT (HR = 0.36, p = 0.00013). HIPEC did not statistically improve survival.
Conclusion: Cure in DSRCT is possible in 5% of patients and is best achieved combining systemic chemotherapy, complete cytoreductive surgery and WAP-RT. Despite aggressive treatment, recurrence is common and targeted therapies are urgently needed.

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1. Introduction

Desmoplastic Small Round Cell Tumor (DSRCT) is a rare disease affecting predominantly children and young adults, with an estimated incidence between 0.2 and 0.5 new cases per million per year [1–4]. Fewer than 900 cases have been reported in the literature since its first description in 1991 [4]. A specific translocation t(11:22)(p13; q12), which fuses the Ewing Sarcoma (EWS) gene to the Wilms' tumor (WT1) gene, is required for a formal diagnosis [5–7]. Abdominal DSRCT has an extremely aggressive clinical course, with more than 90% of patients having synchronous peritoneal metastases (PM) and 47%–53% having synchronous extra-peritoneal metastases (EPM) at diagnosis [8,9]. Despite multimodal treatment including systemic chemotherapy, surgery and additional invasive procedures such as hyperthemic intraperitoneal chemotherapy (HIPEC) or whole abdomino-pelvic radiotherapy (WAP-RT), the prognosis remains poor with a median overall survival (OS) ranging from 14 to 38 months, depending on disease extension and treatment modalities [10–12]. Long-term survival has been reported in 8% of patients with metastatic or locally advanced unresectable soft-tissue sarcoma [13]. Whether this applies to DSCRT is unclear although f long survivors have been reported across all series of DSRCT. In the absence of a large population with enough follow-up, we have no clear information on these patients and potentially on the reasons why their disease never recurred. The aim of the present study was to identify in a nation-wide survey patients with a prolonged survival after DSRCT diagnosis and to identify potential prognostic factors associated with a cure.

2. Methods

2.1. Patient identification and classification

A nation-wide retrospective survey was performed to identify all patients treated for DSRCT in nine expert sarcoma and/or rare peritoneal disease tertiary care centers in France (Gustave Roussy Cancer Campus, Strasbourg University Hospital, Claudius Régaud Institute, West Cancer Institute, South Lyon University Hospital, Bergonié Institute, Paoli-Calmettes Institute, Curie Institute, Leon Bérard Center) between January 1991 and January 2018, by crossing the prospective and retrospective databases of each center. DSRCT diagnosis was based on the identification of the t(11:22)(p13; q12) translocation and/or on the tumor histological features. All patients had a systematic centralized expert pathologist review within the French expert network "*Réseau de Référence en Pathologie des Sarcomes des tissus mous et des viscères*" (RRePs) to confirm the diagnosis. Demographic data, diagnostic circumstances, tumor extension and characteristics, treatment variables and long-term outcome were retrospectively retrieved from the patients' files. Extra-peritoneal metastases (EPM, including lymph node metastases) were diagnosed upon radiological findings. Whenever available, the peritoneal extent of the disease, evaluated peroperatively with the Peritoneal Cancer Index (PCI), was recorded [14]. All patients were retrospectively staged according to the MD Anderson Cancer Center DSRCT staging criteria [15]. The completeness of peritoneal cytoreduction was retrospectively graded according to the Sugarbaker completeness of cytoreduction (CC) score, as follows: CC0, no residual macroscopic disease; CC1, residual nodules smaller than 2.5 mm; CC2, residual nodules between 2.5 mm and 2.5 cm; and CC3, residual nodules greater than 2.5 cm [14]. Surgery was considered macroscopically complete when CC0 or CC1. Surgical complications were retrospectively graded according to the Clavien-Dindo classification [16]. Grade 3 or higher complications were considered severe.

2.2. Patient selection for analysis

Patients with an insufficient follow-up (defined as less than 2 years after diagnosis) were excluded from the analysis. Patients were considered cured if the disease-free interval lasted at least 5 years after the diagnosis or the last recurrence.

2.3. Long-term follow-up

Recurrence was diagnosed based on clinical or radiological findings. Progressive disease was defined as tumor growth documented by imaging analysis (MRI or CT scan) according to RECIST 1.1 [16]. Follow-up data included the date of the most recent follow-up, the patient's status (alive with disease, alive with no evidence of disease, dead), the site of the initial recurrence, and the site of all subsequent recurrences.

2.4. Statistics

Continuous variables are presented as numbers (with percentage), mean (+/− standard deviation) or median (with range). The Gaussian nature of the quantitative variables was assessed graphically and using the Shapiro-Wilk test. Univariate analysis for predictive factors for cure was performed using the Chi-squared and Fisher's exact tests, when appropriate for categorical variables, whereas Mann-Whitney U-tests were used for continuous variables. Survival analyses were performed using the Kaplan-Meier method, and groups compared using the log-rank test, when appropriate. Overall survival (OS) was computed from the date of diagnosis to the date of death or last follow-up, regardless of the cause of death. Progression-free survival (PFS) was computed from the date of surgery (in case of surgery) or the one of beginning of treatment (in case of no surgery) to the date of first recurrence or progression. Analyses were performed with XLSTAT software. A p-value < 0.05 was considered significant.

3. Results

3.1. Demographics

One hundred patients were identified. Eighty-one patients were males (81%) and 19 were females (19%). The median age at diagnosis was 25 years (range: 3–59). The disease was symptomatic in 89 patients. Twenty-five patients (25%) had EPM at the time of diagnosis located mainly in the liver parenchyma (20 patients) in the lung (3 patients including two with associated liver metastases), in the bones (3 patients) (Table 1).

3.2. Induction treatment and response

Eighty patients received upfront chemotherapy and 20 went directly to surgery. Twenty-three different induction regimens were recorded. The most commonly given regimen was a chemotherapy usually used in Ewing's sarcoma (i.e. P6 regimen, VIDE, VDC/IE, VAI, VAC …) in 35 patients (44%). Twenty-eight patients (35%) received an anthracycline-based chemotherapy as usually used in soft-tissue sarcoma (combinations of doxorubicin and/or dacarbazine and/or ifosfamide). Seventeen patients received a cisplatin-based regimen (21%, in combination with bleomycin, epirubicin, 5-fluorouracil, gemcitabine, doxorubicin, ifosfamide, dacarbazine or cyclophosphamide), and one had vincristine alone (1%). Two patients received a combination of bleomycin, etoposide and cisplatin for an initial testicular cancer suspicion. One patient received high-dose chemotherapy with hematopoietic stem cell transplant. The response to chemotherapy was evaluable in 68 patients: progressive disease (PD) in 6 (9%), stable disease (SD) in 18 (26%), and partial response (PR) in 44 (65%). There was no significant difference in terms of response rate regarding the chemotherapy regimens. Eight patients had more than one line of chemotherapy before surgery. (Tables 2 and 3)

Table 1
Characteristics at diagnosis.

Variable		n = 100 (100%)
Sex		
	Male	81 (81%)
	Female	19 (19%)
Mean age, years [SD]		27 [12]
Median age, years [range]		25 [3–59]
WHO performance status		
	0	65 (65%)
	1	17 (17%)
	2	4 (4%)
	N/A	14 (14%)
Median PCI [range]		13 [2–30]
Extra-peritoneal metastases		25(25%)
	Liver metastases	20(20%)
	Lung metastases	3(3%)
	Bone metastases	3(3%)
	Other	3(3%)
More than one EPM site		15 (15%)
MD Anderson stage		
	I	27(27%)
	II	24(24%)
	III	13(13%)
	IV	7(7%)
	N/A	30(30%)
Symptoms		89 (89%)
	Pain	57 (57%)
	Occlusion	2 (2%)
	Bloating	11 (11%)
	Other	19 (19%)
Time of referral to expert center		
	Before any biopsy	18 (18%)
	After initial diagnosis	26 (26%)
	Before surgery	12 (12%)
	After treatment	16 (16%)
	After recurrence	4 (4%)
	Other/unknown	24 (24%)

Abbreviations: WHO, World Health Organization; PCI, peritoneal cancer index; N/A, non-available; EPM, extra-peritoneal metastases.

Table 2
Treatments.

Variable		n = 100 (100%)
Induction chemotherapy		
	Yes	80 (80%)
	No	20 (20%)
Surgery		
	Yes	71 (71%)
	No	29 (29%)
Completeness of cytoreductive surgery		
	CC0	46 (46%)
	CC1	4 (4%)
	CC2/3	21 (21%)
Intraperitoneal chemotherapy		17 (17%)
	HIPEC	15 (15%)
	EPIC	2 (2%)
Intraperitoneal chemotherapy drug		
	Cisplatin	10 (10%)
	Oxaliplatin	6 (6%)
	MMC	6 (6%)
Postoperative WAP-RT		26 (26%)
Postoperative chemotherapy		54 (54%)
	Pre- and postoperative	36 (36%)

Abbreviations: HIPEC, hyperthemic intraperitoneal; chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; MMC, mitomycin; WAP-RT, whole abdomino-pelvic radiotherapy.

Table 3
Predictive factors for cure (univariate analysis).

	Not cure, n = 95 (100%)	Cured, n = 5 (100%)	p
Sex			0.005
Male	80 (84%)	1 (20%)	
Female	15 (16%)	4 (80%)	
Median age, years [range]	25 [3–59]	28 [16–48]	0.62
WHO performance status			0.19
0	61 (64%)	4 (80%)	
1	17 (18%)	0 (0%)	
2	4 (4%)	0 (0%)	
N/A	13 (14%)	1 (20%)	
Median PCI [range]	13 [2–30]	6 [2–9]	0.005
Extra-peritoneal metastases	25 (26%)	0 (0%)	0.19
Liver metastases	20 (21%)	0 (0%)	0.35
Lung metastases	13 (14%)	0 (0%)	0.59
Bone metastases	3 (3%)	0 (0%)	1
Other	3 (3%)	0 (0%)	1
More than one EPM site	15 (15%)	0 (0%)	0.60
MD Anderson stage			0.003
I	22 (23%)	5 (100%)	
II	24 (25%)	0 (0%)	
III	13 (14%)	0 (0%)	
IV	7 (7%)	0 (0%)	
N/A	30 (31%)	0 (0%)	
Symptoms at diagnosis	85 (89%)	4 (80%)	1
Time of referral to expert center			0.51
Before any biopsy	18 (19%)	0 (0%)	
After initial diagnosis	25 (26%)	1 (20%)	
Before surgery	10 (11%)	1 (20%)	
After treatment	16 (17%)	0 (0%)	
After recurrence	3 (4%)	1 (20%)	
Other/unknown	23 (23%)	2 (40%)	
Completeness of cytoreductive surgery			0.005
CC0/1	45 (48%)	5 (100%)	
CC2/3	50 (52%)	0 (0%)	
HIPEC	15 (16%)	0 (0%)	0.65
Preoperative chemotherapy	47 (48%)	4 (80%)	1
Postoperative chemotherapy	53 (56%)	1 (20%)	1
Pre- and postoperative	35 (37%)	3 (38%)	0.47
Postoperative WAP-RT	22 (23%)	4 (80%)	0.003

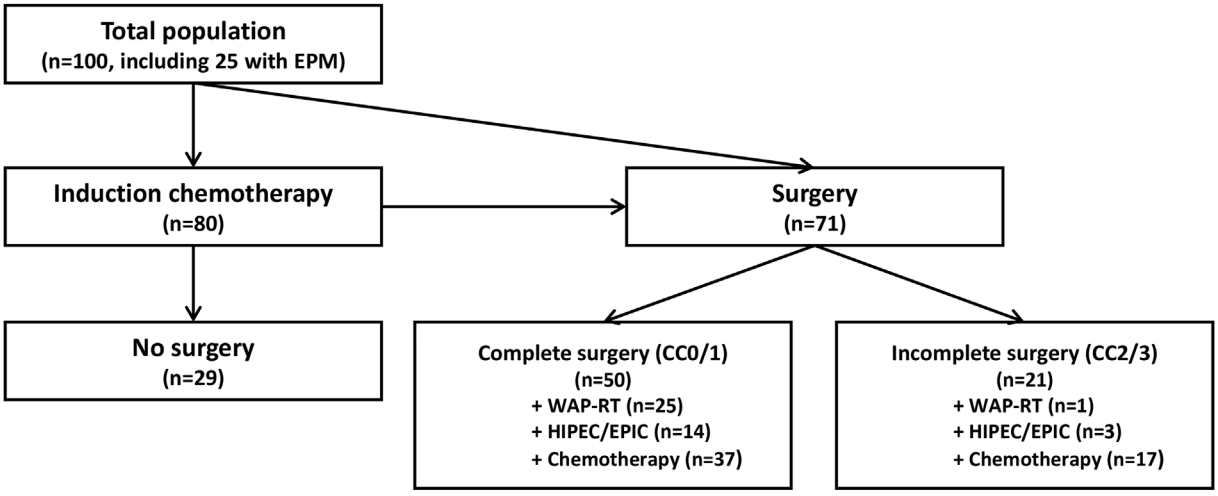
Abbreviation: PCI, peritoneal cancer index; WAP-RT, EPM, extra-peritoneal metastases; WAP-RT, whole abdomino-pelvic radiotherapy.

3.3. Surgery and postoperative complications

Seventy-one patients eventually underwent surgery. Before surgery, 51 patients had chemotherapy (out of 71, 72%) and no patient had radiotherapy preoperatively. Surgery was macroscopically complete (i.e. CC0/1) in 50 patients (out of 71, 70%). Hyperthemic intraperitoneal chemotherapy (HIPEC) was administered during surgery in 15 patients without extra-peritoneal disease and in whom complete cytoreduction (CCR0-1) was achieved (out of 71, 21%). Two patients had early postoperative intraperitoneal chemotherapy with mitomycin and 5-fluorouracil (out of 71, 3%). Four patients had a perioperative chemotherapy, surgery plus HIPEC, and postoperative RT. The postoperative morbidity rate was 16%, including one patient who died postoperatively on postoperative day 40 of hemoperitoneum. The most common severe complications were deep abscess (six patients), digestive anastomotic fistula (two patients), hemoperitoneum (two patients), and limb compartment syndrome (one patient). Fifty-four patients (76%) had postoperative chemotherapy (36 patients (out of 71, 51%) had both pre- and postoperative chemotherapy) and 26 patients (out of 71, 37%) received postoperative whole abdominal RT (at the dose of 30Gy).

3.4. Overall and disease free survival

After a median follow-up of 103 months (range: 23–311), the



Abbreviation : EPM, extra-peritoneal metastases; WAP-RT, whole abdomino-pelvic radiotherapy; HIPEC, hyperthemic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy

Fig. 1. Selection process and treatment flowchart.

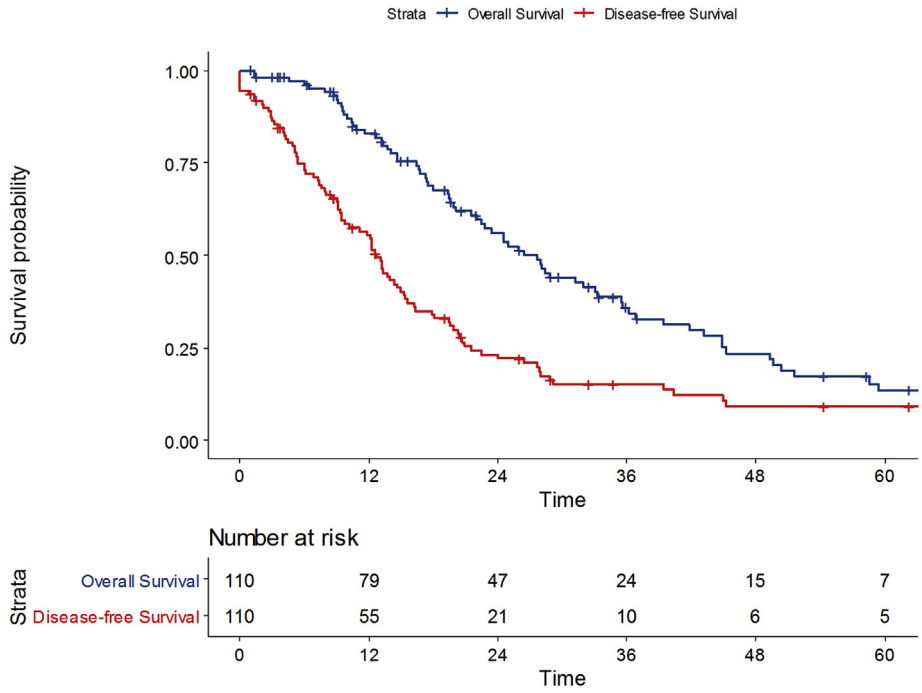


Fig. 2. Overall and disease free survival.

median overall survival (OS) of the entire cohort was 25 months (range: 4–154) and the median PFS was 11 months (range: 1–134). During this follow-up, all patients (n = 50) after incomplete or no surgery died after a median delay of 21 months (range: 4–71). Another 42 patients died after complete surgery (median time of 36 months, range: 9–154). OS rates of the entire cohort were 90% (CI 95% [84–96]) at 1 year, 35% (CI 95% [27–46]) at 3 years, and 12% (CI 95% [7–21]) at 5 years. During this follow-up, 42 out of 50 patients developed recurrence after complete surgery, after a median delay of 12 months (range 2–46). Another 50 patients developed progression after incomplete or no surgery, after a median time of 9 months (range 1–26). The median disease free survival (DFS) of the entire cohort was 11 months (range 1–134). PFS rates were 59% (CI 95% [50–69]) at 1 year, 7% (CI 95% [3–15]) at 3 years, and 6% (CI 95% [3–14]) at 5 years, and 7% (CI 95% [2–12]) at 10 years. No patients ever developed recurrence or died later than after 46 months of follow-up. These results are illustrated in Fig. 1.

3.5. Predictive factors for cure

In the present series, eight patients were disease-free after a median time of 100 months (range 22–139) from the diagnosis of DSRCT among whom, five had more than 5 years of disease-free survival and considered cured. In univariate analysis, predictive factor of being free of disease at 5 years were female sex (HR = 0.49, p = 0.014), median PCI < 12 (HR = 0.32, p = 0.0004), MD Anderson stage I (HR = 0.25, p < 0.0001), complete cytoreductive surgery (i.e. CC0/1, HR = 0.34, p < 0.0001), and postoperative WAP-RT (HR = 0.36, p = 0.00013). The presence of extra-peritoneal metastases did not reach statistical significance if resection was complete. Neither HIPEC or (EPIC did increase statistically the rate of cure (HR = 1.35, p = 0.65).

3.6. Survival with or without surgery

Without surgery (n = 29), median OS was 19 months (range: 4–45) and median PFS was 8 months (range 2–26), with significant difference when compared with patients with surgery ($p < 0.0001$ and $p = 0.04$, respectively). No long-term survivor was recorded in this group. After incomplete surgery (n = 21), median OS was 24 months (range: 12–71) and median PFS was 10 months (range: 1–21), with significant difference when compared with patients with complete surgery ($p = 0.012$ and $p = 0.009$, respectively). No long-term survivor was recorded in this group. After complete surgery (n = 50), median OS was 36 months (range: 9–154) and median PFS was 12 months (range: 1–334). In the later situation, recurrence was documented in 42 patients. The first site of recurrence was the peritoneum in 23 patients (out of 42, 56%), distant in 8 (19%), and mixed (synchronous peritoneal and distant) in 11 (26%). One recurrence site was not retrospectively available. The most common sites of distant metastases were: lymph nodes (four patients), lung (four), liver (three) and bone (three). No long-term survivor was identified in this group of patients with distant recurrence.

4. Discussion

This retrospective study shows that although DSRCT remains a complex disease with a very poor prognosis, cure is possible in a sizeable subset of patients, with 5% of long-term survivors. This rate is similar to the one reported in other patients with metastatic soft-tissue sarcomas [13].

We identified disease-related and treatment-related factors predictive of cure. Disease-related factors were a low PCI (< 12) and the absence of EPM at diagnosis. Treatment-related factors were the ability to achieve a complete of cytoreductive surgery and the realization of a postoperative WAP-RT. These factors were already widely reported in earlier studies, and remain a cornerstone for cure [8,11,17]. An intriguing question is the real value of systemic chemotherapy. Perioperative chemotherapy has proven its prognostic value in Ewing sarcoma [18]. The benefit in DSRCT is more difficult to evaluate [8,17,19]. Nevertheless, it enables patient selection because progressive disease (PD) under chemotherapy remains a strong surrogate for aggressive tumor behavior. In our series, the only patient with initial PD under induction chemotherapy underwent “rescue” surgery. He subsequently experienced dramatic disease relapse in the peritoneum, liver, lung and lymph nodes less than 6 months after surgery despite complete cytoreductive surgery (CC0) and adjuvant chemotherapy (VIDE). The patient died 3 months later. In our opinion, PD under induction chemotherapy should systematically contraindicate subsequent surgery. There are no clinical trials specifically addressing the issue of induction chemotherapy for DSCRT and the best regimen still has to be defined. Treatment either includes chemotherapy extrapolated from Ewing sarcoma regimen (due to the similarities observed in genomics, histology, age, and sex ratio: high-dose cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide and etoposide) or chemotherapy used in soft tissue sarcoma (combination of doxorubicin and ifosfamide). Even if earlier studies reported lesser response rates using doxorubicin-based chemotherapy, we found no major differences in response rates between various regimens in the present series and increasing the burden of chemotherapy has never proven to add any survival benefit in DSRCT [2,4,8,19]. Despite very aggressive frontline systemic treatments, more than 90% of patients died of disease recurrence, suggesting that we failed to eradicate hidden tumor cells and/or failed to reach sanctuaries. Even induction myeloablative chemotherapy followed by autologous bone marrow or peripheral stem cell rescue has been employed, but with limited success [20]. Minimizing the number of agents for tailoring subsequent regimens based on response to the initial therapy, and lowering the chemotherapy-induced toxicity is therefore seducing. This is very important, especially in adult patients in whom systemic treatments are less well tolerated than in their younger counterparts. Without clearly proven survival benefit, induction chemotherapy in patients with DSRCT could aim preoperatively to decrease the tumor bulk, and thereby select patients with favorable tumor behavior [21]. The regimen may be adapted to the needs of the surgeon to make the disease resectable, with the idea of keeping available drugs in case of subsequent relapse and avoiding chemotherapy-related undue toxicity. The benefit of adjuvant chemotherapy is still unknown in DSRCT. In our series, it did not seem to prevent disease recurrence and two patients out of the five cured did not receive any adjuvant chemotherapy. Yet, adjuvant strategy based on post-treatment percentage of necrosis was reported with better outcome and may be more appealing [18].

In our experience, a cure cannot be achieved with chemotherapy alone or after incomplete surgery. Nevertheless, questions about surgery remain unanswered and should be subject of further studies. First, what benefit can we expect from surgical debulking of an unresectable peritoneal disease or when MEP are present. Even if not bringing any survival benefit, it could prevent further complication of a bulky disease or treat symptoms. Another major surgical question is, considering the poor prognosis of DSRCT, the justification of mutilating pelvic surgery in young adults. Knowing that only one out of the seven patients cured in our series had a PCI above 12, we suggest that this cut-off might help discriminating the potential candidates for extensive surgery. We found no clear benefit of adding HIPEC in our series, and currently we do not perform it anymore until further prospective data are available. Finally, not knowing the origin of the disease, surgeons often experience difficulties for identifying the route of lymphatic drainage and for doing a complete lymph node resection, with in consequence lymph nodes recurrence being a frequent pattern of failure. Tumor recurrence and progression is common in DSRCT. The pattern of failure after complete surgery is informative because despite macroscopically complete surgery and whatever the associated treatment (systemic chemotherapy, HIPEC and/or WAP-RT), the first recurrence site is the peritoneum in 88% of cases, demonstrating our inability to eradicate microscopic residual disease despite very aggressive treatments. Preliminary results from a phase 2 trial suggested cisplatin-based HIPEC after complete cytoreductive surgery could prevent peritoneal recurrence in selected patients with DSRCT [21]. We found in our series contradictory results, with none of the 10 patients who had this cisplatin-based HIPEC among the five patients cured. Until we have comparative data, we cannot make any recommendation on the value of HIPEC in this disease.

The limitation of this retrospective analysis is still the small number of patients treated in numerous centers over a long period and the heterogeneity in terms of treatment modalities that did not allow providing a high level of evidence. However, by crossing different national databases, this study brings an exhaustive list of patients treated with curative intent since 1991. Although we believe the next step should be to develop an international centralized prospective database, we have the feeling we herein came to the limits of what clinical data could bring in this disease and that biological research is urgently needed. DSRCT is characterized by the fusion of the WT1 gene and the EWS gene within the t(11; 22)(p13; q12) translocation but has a largely unknown activating pathway. . Most second-line treatment data coming from small retrospective series, using off-labeled drugs without translational research, the incorporation of molecular information including whole genome sequencing and immune-profiling to further select targeted therapy is probably the key to improve survival in the future [19,22,23].

5. Conclusion

Cure is possible in 5% of patients treated for a DSRCT as it has been reported in patients with other metastatic soft-tissue sarcomas. The best available treatment should combine systemic perioperative chemotherapy, complete cytoreductive surgery and postoperative WAP-RT.

Despite aggressive treatment, recurrence and progression is common and targeted treatments are urgently needed although no target has been identified yet.

Conflicts of interest

Dr. Mir has acted as consultant for Amgen, Bristol-Myers Squibb, Eli-Lilly, Ipsen, Lundbeck, Pfizer, Roche, Servier and Vifor.

Dr Blay received honoraria and research support from Roche, Novartis, GSK, Lilly, BayerMSD, Pharmamar, AstraZeneca, BMS, Ignyta, AROG, and Deciphera

Dr. Orbach has acted consultant consultant for Bayer.

Other authors report no conflicts of interest.

Source of support

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.04.002.

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