Original Article

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Macroscopically complete excision is a beneficial strategy for selected patients with peritoneal sarcomatosis

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SUMMARY The occurrence of peritoneal sarcomatosis (PS) in patients with retroperitoneal sarcoma (RPS) indicates a poor prognosis. However, the appropriate treatment modality remains unclear. This study aimed to identify its prognostic factors and further explore the role of macroscopically complete excision (CE) in the management of PS. A retrospective database was established to evaluate patients with RPS who underwent resection between January 2011 and January 2019. Univariate and multivariate survival analyses were performed to analyze the prognostic factors and identify the population that will optimally benefit from CE. This study included a total of 49 patients with PS from 211 patients with RPS, and 34 (69.4%) patients of whom with PS underwent CE successfully. The median follow-up time was 36.0 months. There were 8 patients excluded because of loss to follow-up (n = 4) or death from complications within 90 days postoperatively (n = 4). The CE group had a marginally better prognosis compared to the macroscopically incomplete excision (IE) group (median disease-specific survival: 20 months *vs.* 8 months). Multivariate survival analysis demonstrated that completeness of operation (CE *vs.* IE) was the only independent prognostic factor in PS patients (P = 0.042). There was no significant difference in the overall complications between the CE and IE groups (P = 0.205). In conclusion, completeness of macroscopical excision is an independent prognostic predictor of PS. If technically possible, CE is a feasible strategy to improve the prognosis of selected patients with PS.

Keywords peritoneal sarcomatosis, prognostic factors, macroscopically complete excision, survival benefit, appropriate patients

1. Introduction

Retroperitoneal sarcoma (RPS) refers to several categories of rare tumors that originate from the retroperitoneal mesenchymal tissue. RPS accounts for approximately 16% of all soft tissue sarcoma cases (*1,2*).

Peritoneal sarcomatosis (PS) is a state of intraperitoneal dissemination of sarcomas. PS is rare and occurs only in approximately 10% of patients with primary RPS disease (*3*). However, PS is highly common in patients with recurrent RPS disease, occurring in 35-82% of patients (*4,5*). The presence of pathologically confirmed lesions on the surface of the peritoneum or intraperitoneal viscera is considered as PS. It can be a spontaneous phenomenon or caused by iatrogenic factors (*6*). Traditionally, PS often indicates end-stage disease, with a median survival of less than 1 year (*7*).

However, data on PS are limited owing to its rarity and complexity, and thus the management of PS remains controversial. Most pathological subtypes of RPS are not sensitive to radiotherapy and chemotherapy (*8*), and thus, surgical resection is the primary treatment modality. However, the role of complete resection for PS is still controversial. Some researchers believe that surgery should be restricted to palliative intervention according to the symptoms, with the goal of avoiding complications and preserving function (*9*), while others support that macroscopically complete resection can significantly improve the prognosis of patients (*6,10*).

Therefore, this study aimed to analyze the prognostic factors, explore the benefits of macroscopically complete excision (CE) for patients with PS, and identify the population who will optimally benefit from CE.

2. Patients and Methods

2.1. Study design and patients

Using the RPS database at Peking University Cancer

Hospital Sarcoma Center, we identified 211 patients who underwent surgery for RPS between January 2011 and January 2019. Among these, the clinicopathological data of 49 patients with PS were collected and analyzed. The patients were defined as primary and recurrent patients according to whether they had undergone RPS-associated surgical treatment before admission or not. The RPS pathological subtypes were classified according to the 2020 World Health Organization criteria for soft tissue tumors (*11*). PS nodules were carefully assessed through intraoperative exploration and postoperative pathological examination. Pathological diagnoses were reviewed by two experienced pathologists specializing in sarcomas. Disagreements were resolved by discussion between them.

The study variables included sex, age, body mass index (BMI), pathological subtypes, operation history (primary or recurrent), the sum of the largest diameter (SLD) of tumors with a diameter more than 1 cm on imaging, ascites, number of nodules, the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade (*12*).

This study was approved by the ethics committee of the Peking University Cancer Hospital and was conducted according to the tenets of the Declaration of Helsinki. All patients in our study provided written informed consent for data collection.

2.2. Surgical outcomes and follow-up

Current surgeries were classified into complete excision (CE) and incomplete excision (IE). CE was defined as the status of removal of all macroscopic disease (R0/R1). IE was defined as the status of macroscopic residual disease (R2) (*13*). Additionally, piecemeal excision and/or tumor rupture intraoperatively were also considered as IE owing to their high risk for residual disease. Operation reports, immediate postoperative imaging and pathological reports were carefully reviewed and checked to confirm the completeness according to above definition.

Postoperative complications occurring within 90 days (POD 90) of the procedure were graded according to Clavien-Dindo classification (*13*). Postoperative pancreatic fistula was diagnosed according to the criterion of 2016 International Study Group on Pancreatic Surgery (*14*). The patients were prospectively followed with regular telephone follow-up and outpatient follow-up including physical examination, ultrasonography, abdominopelvic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) every 3 months for the first 2 years, every 6 months for the subsequent three years, and yearly thereafter.

2.3. Statistical analysis

The primary endpoint was disease-specific survival (DSS), defined as death due to tumor progression. Survival time was calculated from the time of operation to the concerning event. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. The optimal cut-points for continuous variables were determined by using the maximally selected rank statistics (*15,16*). The Cox proportional hazards regression model was used for the univariate and multivariate prognostic analysis (enter method). Variables with $P < 0.1$ in the univariate analysis and clinically significant variables were included in the multivariate analysis. Comparisons of continuous variables were performed by Wilcoxon's rank-sum test, and the comparisons of categorical variables were performed by Pearson's Chi-square test, continuity correction Chi-square test, or Fisher's exact test, as appropriate. To identify the PS patients who will optimally benefit from CE, subgroup analysis and *P* for interaction were also calculated (*17*). All statistical analyses were performed using SPSS version 26.0 (IBM) and R version 4.0.5 *(http://www.r-project.org/)* with packages of "survival", "surminer", "maxstat", , and "maxstat". Statistical significance was set at a two-sided $P < 0.05$.

3. Results

Among the 211 screened patients with RPS, 49 (23.2%) patients with PS (29 men and 20 women; median age, 50 years; range, 16-86 years) were included in this study (Figure S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=86*). Of these patients, 15 (30.6%) and 34 (69.4%) were identified as primary and recurrent patients, respectively. The incidence rate of PS was 13.0% (15/115) and 35.4% (34/96) in the primary and recurrent patients, respectively. The clinicopathological characteristics are shown in Table 1. The most common pathological subtypes were dedifferentiated liposarcoma, well-differentiated liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, and synovial sarcoma. All pathological subtypes are listed in Table S1 (*http://www.biosciencetrends.com/action/getSupplementalData.php?ID=86*). The optimal cut-off values for "age", "BMI", and "SLD" were 66 years old, 27 kg/m^2, and 20 cm, respectively.

In total, 34 of the 49 patients (69.4%) with PS underwent CE successfully. Reasons resulting in IE included wide dissemination ($n = 6$), superior mesenteric artery invasion ($n = 3$), abdominal aorta invasion ($n = 2$), bilateral kidney invasion ($n = 1$), piecemeal resection ($n = 2$), and tumor rupture ($n = 1$). All the patients underwent multivisceral resection (MVR) with at least one involved organ resection. The detailed information including initial and current surgeries is summarized in Table 2.

Table 1. Patient characteristics

	Total (n = 49)	CE (n = 34)	IE (n = 15)	P
Sex				0.236[a]
Female	20	12	8	
Male	29	22	7	
Age (median [range], years)	50.0 [16.0-86.0]	48.0 [16.0-78.0]	51.0 [25.0-86.0]	0.737[c]
≥ 66	8	6	2	1[b]
< 66	41	28	13	
Operation history				0.951[b]
Primary patients	15	11	4	
Recurrent patients	34	23	11	
BMI (median [range], kg/m^2)	22.6 [16.9-39.0]	22.3 [17.8-35.5]	24.5 [16.9-39.0]	0.233[c]
≥ 27	10	6	4	0.736[b]
< 27	39	28	11	
SLD (median [range], cm)	27.0 [6.0-69.0]	21.0 [10.0-36.0]	29.0 [6.0-69.0]	0.068[c]
≥ 20	35	22	13	0.220[b]
< 20	14	12	2	
Ascites				1[b]
Yes	10	7	3	
No	39	27	12	
LPS				0.371[a]
Yes	28	18	10	
No	21	16	5	
FNCLCC grade				0.743[a]
G1, G2	18	13	5	
G3	31	21	10	
Number of nodules				0.667[b]
≥ 7	10	8	2	
< 7	39	26	13	

[a]Pearson's Chi-square test; [b]continuity correction Chi-square test; [c]Wilcoxon's rank-sum test. CE, macroscopically complete excision; IE, macroscopically incomplete excision; SLD, the sum of the largest diameter; LPS, liposarcoma; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer.

Table 2. Surgical results in patients with peritoneal sarcomatosis

	CE (n = 34)	IE (n = 15)	P
History of surgery			0.951[b]
Primary surgery	11 (32.4%)	4 (26.7%)	
Recurrent surgery	23 (67.6%)	11 (73.3%)	
Initial surgical method of recurrent patients[a]			0.825[c]
En-bloc resection	3 (13.0%)	1 (6.7%)	
Simple tumor resection	18 (78.3%)	8 (53.3%)	
Macroscopically incomplete resection	2 (8.7%)	2 (13.3%)	
Multivisceral resection	34 (100%)	15 (100%)	
Number of resected organs of the current surgery (median [range])	4.5 [1-13]	4 [1-10]	0.371[d]
Common resected organs of the current surgery			0.002[c]
Colon	27 (79.4%)	14 (93.3%)	
Kidney	18 (52.9%)	2 (13.3%)	
Small bowl	10 (29.4%)	6 (40.0%)	
Pancreas	11 (32.4%)	5 (33.3%)	
Abdominal wall	9 (26.5%)	3 (20.0%)	
Resection of major vessels and revascularization	5 (14.7%)	0 (0%)	

[a]Only the recurrent patients need to be considered for their initial surgery; [b]continuity correction Chi-square test; [c]Fisher's exact test; [d]Wilcoxon's rank-sum test. CE, macroscopically complete excision; IE, macroscopically incomplete excision.

There were 8 patients excluded from survival analysis because of loss to follow-up (n = 4) or death from complications within 90 days after surgery (n = 4). The median follow-up time was 36.0 months. Overall, the median DSS of the patients with PS was 15 months (95% confidence interval [CI], 9-34). The 3- and 5-year DSS rates were 19.9% and 0, respectively. The median DSS was 20 months and 8 months in patients with PS in whom CE and IE were performed, respectively. The 3-year DSS was 25.1% in the CE group, and 10.3% in the IE group (log-rank P = 0.077, Figure 1). Besides, the multivariate analysis showed that completeness of operation (CE *vs.* IE) was the only independent prognostic factor in the patients with PS (P = 0.042)

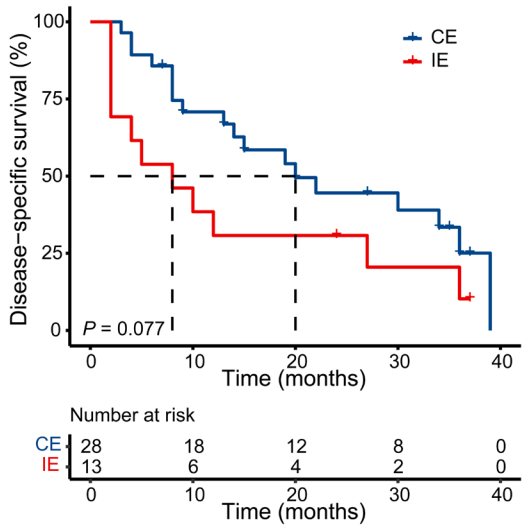

Figure 1. Survival of patients with peritoneal sarcomatosis and survival benefit from macroscopically complete excision.

(Table 3).

We further investigated the prognosis of the subgroups and interactions between treatment and sex, age, operations, BMI, SLD, ascites, LPS, and FNCLCC grade. Overall, CE lowered the risk of DSS by 48% (hazard ratio [HR], 0.52; 95% CI, 0.24-1.11). This effect was significant in patients with recurrent disease (HR, 0.28; 95% CI, 0.10-0.74), non-LPS (HR, 0.15; 95% CI, 0.04-0.57), and FNCLCC grade 3 (HR, 0.34; 95% CI, 0.13-0.88). Furthermore, differences by interaction were particularly robust in the covariates of operation history type (*P* for interaction = 0.026), and FNCLCC grade (*P* for interaction = 0.005) (Figure 2).

To evaluate the perioperative safety of CE, we analyzed the outcomes of patients with PS within 90 days postoperatively. Overall, the rate of 90 days postoperative mortality was 8.2% (4/49), and the rate of severe morbidity (Clavien-Dindo ≥ III) was 28.6% (14/49). Common complications included abdominal

Table 3. Univariate and multivariate survival analysis in patients with peritoneal sarcomatosis

	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Age (≥ 66 *vs.* < 66, years)	0.771	1.14 (0.46-2.84)	0.814	1.16 (0.33-4.13)
Male *vs.* Female	0.576	1.25 (0.57-2.71)	0.605	1.31 (0.48-3.58)
BMI (< 27 *vs.* ≥ 27, kg/m^2)	0.986	0.99 (0.42-2.34)	0.933	0.95 (0.32-2.85)
Completeness of excision (IE *vs.* CE)	0.077	1.99 (0.93-4.25)	0.042	2.66 (1.04-6.83)
Operation history (recurrent *vs.* primary)	0.938	0.97 (0.44-2.15)	0.616	1.34 (0.43-4.13)
Ascites (yes *vs.* no)	0.242	1.68 (0.71-3.98)	0.606	0.72 (0.21-2.49)
FNCLCC grade				
G2 *vs.* G1	0.232	3.56 (0.44-28.44)	0.282	3.69 (0.34-39.89)
G3 *vs.* G1	0.102	5.46 (0.71-41.78)	0.13	5.46 (0.61-49.05)
SLD (≥ 20 *vs.* < 20, cm)	0.209	1.79 (0.72-4.44)	0.412	1.66 (0.50-5.54)
Pathology (LPS *vs.* Non-LPS)	0.210	1.61 (0.77-3.38)	0.428	1.55 (0.52-4.61)
Number of nodules (≥ 7 *vs.* < 7)	0.223	1.67 (0.7-3.8)	0.523	1.59 (0.38-6.55)

HR, hazard ratio; CI, confidence interval; CE, macroscopically complete excision; IE, macroscopically incomplete excision; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; SLD, the sum of the largest diameter; LPS, liposarcoma.

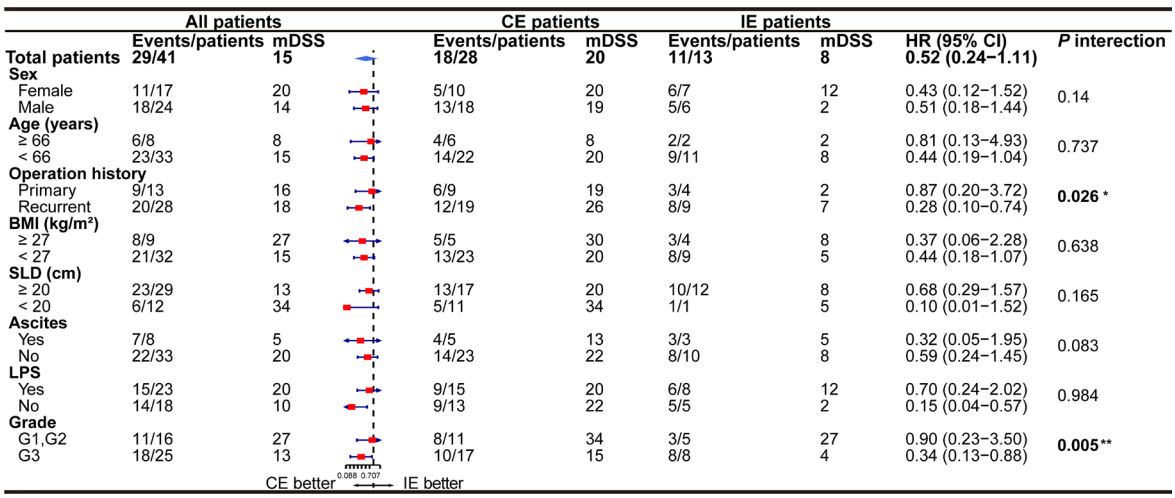

Figure 2. Disease-specific survival by the completeness of macroscopical excision in each subgroup. *P for interaction < 0.05; **P for interaction < 0.01; CE, macroscopically complete excision; IE, macroscopically incomplete excision; BMI, body mass index; SLD, the sum of the largest diameter; LPS, liposarcoma; HR, hazard ratio; CI, confidence interval; mDSS, median disease-specific survival.

Table 4. Postoperative outcomes

	Total (*n* = 49)	CE (*n* = 34)	IE (*n* = 15)	*P*
POD 90 complications				0.205
Yes	26 (53.1%)	16 (47.1%)	10 (66.7%)	
No	23 (46.9%)	18 (52.9%)	5 (33.3%)	
POD 90 complications grade				0.556
Clavien-Dindo I-II	12 (46.2%)	6 (37.5%)	6 (60.0%)	
Clavien-Dindo III-IV	10 (38.5%)	7 (43.8%)	3 (30.0%)	
Clavien-Dindo V	4 (15.4%)	3 (18.8%)	1 (10.0%)	
Classification of major complications				
Hemorrhage	1 (2.0%)	1 (2.9%)	0 (0%)	
Abdominal infection	4 (8.2%)	3 (8.8%)	1 (6.7%)	
Urinary retention/urinary tract irritation	2 (4.1%)	2 (5.9%)	0 (0%)	
Coagulation disorder	1 (2.0%)	0 (0%)	1 (6.7%)	
Lower limb dysfunction	1 (2.0%)	1 (2.9%)	0 (0%)	
Incision infection	4 (8.2%)	1 (2.9%)	3 (20.0%)	
Delayed gastric emptying	1 (2.0%)	1 (2.9%)	0 (0%)	
Anastomotic fistula (grade B)	2 (4.1%)	0 (0%)	2 (13.3%)	
Pancreatic fistula (biochemical leakage)	1 (2.0%)	0 (0%)	1 (6.7%)	
Pancreatic fistula (grade B)	4 (8.2%)	4 (11.8%)	0 (0%)	
Pancreatic fistula (grade C)	1 (2.0%)	0 (0%)	1 (6.7%)	
Organ dysfunction (heart, lung, kidney)	4 (8.2%)	3 (8.8%)	1 (6.7%)	

CE, macroscopically complete excision; IE, macroscopically incomplete excision; POD, postoperative day.

infection (*n* = 4, 8.2%), incision infection (*n* = 4, 8.2%), grade B pancreatic fistula (*n* = 4, 8.2%) and organ dysfunction (*n* = 4, 8.2%), *etc.* The overall complication rate was 47.1% in the CE group and 66.7% in the IE group. There was no significant difference between the two groups (*P* = 0.205). Specifically, the main complications in the CE group were grade III-IV complications, while grade I-II complications were more commonly seen in the IE group. However, there was no significant difference in the complication rate between the two groups (*P* = 0.556). The occurrence of postoperative complications in PS patients is shown in Table 4.

4. Discussion

The onset of RPS is usually insidious with a large volume and obvious heterogeneity in histology. Theoretically, RPS originates from and should be restricted to the retroperitoneal space. However, sometimes the anatomical boundary is broken through spontaneously or iatrogenically, and lesions occur on the surface of the peritoneum or intraperitoneal viscera. Such phenomenon is regarded as PS (*20*).

PS is not a very rare phenomenon in patients with RPS. According to our data, its incidence rate was 13.0% (15/115) and 35.4% (34/96) in the primary and recurrent RPS patients, respectively. Traditionally, as peritoneal carcinomatosis of gastric cancer or colon cancer, PS is regarded as metastasis of RPS, indicating end-stage disease, with a poor outcome. In this case, systemic therapy is usually the first choice and surgery is perceived as conferring little survival benefit. However, differences of biological behavior between RPS and carcinoma should not be ignored. Unlike carcinoma, the intra-abdominal recurrence, rather than lymph node metastasis and distant metastasis, is the main cause of treatment failure in RPS (*18,19*). Unlike the diffusely miliary distribution of peritoneal carcinomatosis, the distribution of PS is often nodular and limited. In addition, unlike the overall high response rate to systemic therapy of carcinoma, few subtypes of RPS are sensitive to systemic therapy. Therefore, the treatment modality of PS remains worth exploring.

The effect of systemic therapy for advanced RPS including PS is unsatisfactory. The response rate is in the 5-25% range, and median progression-free survival is in the 2~6 months range (*20*). The combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment of peritoneal carcinomatosis. However, Baratti *et al.* reported that the combination of CRS and HIPEC does not compare favorably to those of CRS alone in PS (*21*). Another systematic review in 2011, which included eight prospective and one randomized trial representing 240 patients, concluded that there is a lack of adequate evidence to support that the combination of intraperitoneal chemotherapy and CRS is superior to CRS alone in PS (*22*). Contrarily, several studies reported that the completeness of CRS predicted prognosis in multivariate analysis, indicating that local disease control affected the survival significantly (*4,23*).

Surgical treatment is the mainstay of RPS. It seems that if technically possible, CE remains the most effective treatment of PS. Considering the large anatomical relations with adjacent organs within the abdominal cavity, it is challenging to accurately confirm

negative microscopic margins in RPS. Therefore, in many studies as well as the present study, the status of "removal of all macroscopic disease" was regarded as CE (*24,25*). Technically, CE is feasible to RPS with PS, while its effect remains controversial. One of the controversies is whether PS patients can benefit from CE, and the other one is its safety.

Karakousis *et al.* reported a CE rate of 64% in patients with PS, and patients with CE had a better prognosis than those with IE (median OS: 22.8 *vs.* 8.6) (*10*). A similar result was observed in the study by Sugarbaker *et al.*, with a CE rate of 62.8%. CE improved the prognosis significantly ($P = 0.005$), with the mortality and morbidity of 7% and 19%, respectively (*4*). In the study by Baratti *et al.*, the rate of CE was 75.7%, with an operative mortality of 3.7% and a morbidity of 21.6% (POD 30, National Cancer Institute Common Terminology Criteria) (*21*). Our results also revealed that a large proportion of patients with PS could achieve CE (69.4%). The survival benefit of CE was observed (median DSS: 20 months *vs.* 8 months), and CE is the only independent prognostic factor of PS in the multivariate analysis. Exploring further, recurrent patients and patients with FNCLCC grade 3 disease may benefit more from CE. As for the safety, the mortality and major morbidity of the present study was 8.2% and 28.6%, respectively, similar to literature reports.

According to the consensus from Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG), the role of surgery for multifocal intra-abdominal metastases is limited to palliative intervention as dictated by symptoms (*20*). However, a series of studies as well as the present study revealed that aggressive surgery may provide survival benefits for selected patients. Considering the complexity, it is recommended that the indication of surgery was discussed by a multidisciplinary team of sarcoma specialists, based on comprehensive consideration. A number of disease- and patient-specific factors should be considered during the decision-making, including if distant metastases exist, if life-threatening conditions exist, if macroscopically complete resection is possible, the pathology, the interval between previous surgery and recurrence, the effect of systemic treatment, *etc.* Generally speaking, if there is no complete resection possibility or rapid recurrence from previous complete resection, surgery should be considered cautiously and limited to palliate severe symptoms. Otherwise, "CE-intent surgery" could be considered aggressively.

The number of lesions was also one of the factors that should be considered, combined with others. Anaya *et al.* found that patients with more than 7 tumors have the worst prognosis (*26*). However, we did not reproduce this significant difference in multivariate analysis ($P = 0.523$). It is worth noting that sometimes it was difficult to confirm the number of lesions (especially small lesions) before surgery. According to our data, only in 44.9% (22/49) of patients, the status of PS could be detected by CT/MRI preoperatively. Therefore, more often, the accurate number of lesions had to be confirmed during the surgery. The result of the present study indicated that when PS was found incidentally during the surgery, it is preferred to pursue CE rather than immediately giving up to palliative resection, if technically possible.

Surgical procedures of RPS are challenging. No matter curative-intent surgery or palliative-intent surgery frequently requires a complex, multivisceral resection (*27*). In the present study, all patients of RPS with PS underwent MVR, referring to multiple specialties including gastrointestinal surgery, hepatopancreatobiliary surgery, urinary surgery, and vascular surgery, *etc.* The goal of the surgical cytoreduction was to remove all visible tumors. However, due to various reasons, sometimes it was impossible to achieve CE. In the present study, the commonest reasons resulting in IE were widespread tumors, anatomical restriction, and piecemeal resection (or tumor rupture). Surgeons had to balance the completeness and security as well as the quality of life individually. Owing to the rarity and complexity, a great number of studies have validated the volume- outcome relationship in RPS, thus patients were strongly recommended to be admitted to a specialized sarcoma center for treatment (*8,28,29*).

This study had certain limitations. First, the retrospective design may have produced biases and resulted in weaker evidence. However, owing to the rarity and the complexity of PS, it is difficult to carry out prospective randomized controlled studies with a large sample size. Second, to minimize the interference of surgery-related factors on statistical analysis, we used data from a single center to ensure the consistency of selection criteria and surgical techniques. However, this also limited the sample size. Nonetheless, through rigorous quality control and analysis, we minimized the influence of bias and confounding factors as much as possible. Thus, we believe that our findings can be helpful for patient assessment and decision-making for treatment. Further studies with a prospective design and a larger sample size are required to validate our findings.

In conclusion, the completeness of macroscopical excision is an independent prognostic factor of PS. If technically possible, CE is a feasible surgical strategy that can improve the prognosis of peritoneal sarcomatosis safely in professional sarcoma centers.

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