Surgical treatment of recurrent retroperitoneal sarcoma in its different patterns: a 15-years' two-centers experience

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Abstract

Introduction:

Few data are available about the role of surgery in the treatment of retroperitoneal sarcoma (RPS) recurrences. We herein report the short- and mid-term outcomes of patients who underwent surgical treatment of RPS recurrences at two Italian centers.

Materials and Methods

From January 2005 to January 2020, 33 patients underwent surgical treatment of isolated locally recurrent RPS (LR group), locally recurrent RPS associated with the presence of distant recurrence (LR + DM group), and distant-only recurrent RPS (DM group). Data regarding pre-, intra-, post-operative course, and follow-up, were retrospectively analyzed and compared.

Results

LR-group was composed of 15 patients, LR + DM group of 9 patients, and DM group of 9 patients. During the follow-up, 78.5% of the LR group, 77.8% of the DM group and 100% of the LR + DM group ($p = 0.244$) experienced a second recurrence. No differences in the mean disease-free survival ($p = 0.127$), overall survival (OS) ($p = 0.165$) was reported between the three groups. Repeated surgery was an independent factor affecting survival in multivariate analysis ($p = 0.01$).

Conclusions

A surgical treatment of RPS recurrences should always be taken into consideration, also in metastatic patients and/or in those who have already undergone surgery, because this approach may offer longer survival.

Introduction

Sarcomas represent a rare and heterogeneous group of diseases, accounting for 1% of all malignancies, and including more than fifty different histotypes. Approximately 20% of soft tissue sarcomas arise from intra-abdominal or retroperitoneal sites [1, 2]. Primary surgery is the mainstay of curative therapy and the "en bloc" compartment is critical for negative margins and cure. However, overall recurrence is quite common (up to 40% at 5-years overall) following resection of retroperitoneal sarcoma (RPS) [3]. Histologic type may predict the pattern of recurrence; we observe a broad spectrum of possibilities, ranging from a very low recurrence rate to a propensity for local recurrence to predominantly distant relapse. Distant relapses are usually hematogenous, like lung or liver metastases, but intra-abdominal metastases are also possible [4]. In this setting, multidisciplinary management is mandatory, although

the existing literature on repeated surgery is limited by the rarity and heterogeneity of these diseases and it mainly consisted of case series or small trials with a complete lack of randomized clinical trials. Some collaborative groups, such as the Trans-Atlantic RPS Working group, have studied this issue in clinical trials and have improved several aspects of the approach to this family of pathology [5]. However, due to very poor evidence, a standard treatment does not exist, especially for metastatic recurrent RPS.

This study aims to evaluate the short and mid-term outcomes of patients who underwent surgical treatment of local, distant or both RPS recurrences in two Italian Institutions, reporting our 15-year experience and discussing the role of surgery in these scenarios, also evaluating the possible role of repeated treatments for RPS recurrences and risk factors that affect survival in this setting.

Materials And Methods

Clinical data of patients that underwent surgical treatment in Pisa and Pavia hospitals from January 2005 to January 2020 for RPS, and prospectively collected in the Institutional databases, were retrospectively evaluated. Inclusion criteria were: patients who underwent surgical treatment of the first recurrence (single or multiple local metachronous recurrences and/or distant metastases), after previous radical surgery of all histotypes of RPS, with the exclusion of Ewing sarcomas, alveolar/embryonal rhabdomyosarcomas, desmoid fibromatosis, gynaecological sarcomas. Only procedures performed to obtain a macroscopically radical treatment with curative intent were included.

The study sample was then divided into three groups according to the site of recurrent disease at the time of the first recurrence: local recurrence (LR), distant recurrence only (DR), or both local and distant recurrence (LR + DR) based on the review of Computer Tomography imaging before surgery.

Pre-operative included variables were age, gender, body mass index (BMI), ASA (American Society of Anesthesiologists) score, localization of the primary RPS, type of surgery of primary tumor (simple removal or compartmental surgery), histological characteristics, pT stage of AJCC system 8th edition and the interval between primary treatment and recurrence.

Perioperative data included the type of surgical procedure depending on the type and localization of RPS recurrence (simple removal, or removal plus "en-bloc" organ resection, or partial removal plus intraoperative thermal ablation), operative time, rate of positive margin, hospital stay, postoperative complications also expressed by Clavien-Dindo classification [6] and 30-day mortality rate. Follow-up information was obtained by clinical examination and radiological imaging: it included the follow-up period, the rate of use of chemotherapy in the peri-operative period, chemotherapy scheme in the peri-operative period, possible second relapse and further surgery or interventional procedures (thermal ablation), the number of nodules, disease-free survival (DFS) expressed as the interval between recurrence surgery and the development of a further relapse and overall survival (OS).

Although all patients have been followed up by oncologists, in the first period of our experience the pre-operative multidisciplinary discussion of these surgical cases was not the standard, and an appropriate

multidisciplinary team was created only in 2009.

Statistical analysis

For the data analysis, the Chi-square test was used to define associations between categorical factors and surgical groups. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using the ANOVA test. Variables with abnormal distribution were expressed as median and compared using the Kruskal- Wallis Test. Survival was compared using Kaplan–Meier curves and log-rank test. Univariate analyses were performed to determine which variables were associated with postoperative mortality and survival; the variables with a p-value < 0.20 at the univariate analysis were subjected to multivariate analysis using the Cox regression method and the results were provided in terms of hazard ratio (HR). A p-value ≤ 0.05 was considered statistically significant. The statistical analysis was performed using SPSS (Statistical Production and Service Solution for Windows, SPSS Inc., Chicago, IL, USA), version 24.

Results

From a pool of fifty-eight patients with RPS managed in the two Italian centers during the study period, thirty-three cases met the inclusion criteria and were included in the analysis. Fifteen (45.4%) had isolated recurrence (LR group), nine (27.3%) had distant metastasis recurrent (DM group) whereas the remaining nine cases (27.3%) had both local plus distant relapse (LR + DM group). Demographic and pre-operative results were showed in Table 1.

Table 1
Baseline characteristics

	LR-group(n = 15)	DM-group (n = 9)	LR + DM-group (n = 9)	P value
Age (years),mean ± SD	61.87 ± 13.90	66.67 ± 12.01	62.33 ± 16.73	0.709
BMI (kg/m^2), mean ± SD	29.91 ± 3.20	28.27 ± 4.30	26.53 ± 5.30	0.347
Male: Famale (%)	5:10 (33.3:66.7)	4:5 (44.4:55.6)	5:4 (55.6:44.4)	0.560
ASA score, n (%)	0	0	0	0.975
ASA I	5 (33.3%)	2 (22.2%)	3 (33.3%)	
ASA II	8 (53.3%)	6 (66.7%)	5 (55.6%)	
ASA III	2 (13.3%)	1 (11.1%)	1 (11.1%)	
ASA IV				
Localization of primary RPS (%)	0 (0.0%)	1 (11.1%)	3 (33.3%)	0.343
Mesentery	1 (6.7%)	1 (11.1%)	0 (0.0%)	
Pelvis	6 (40.0%)	3 (33.3%)	2 (22.2%)	
Right retroperitoneum	8 (53.3%)	4 (44.4%)	4 (44.4%)	
Left retroperitoneum				
pT staging of primary RPS (%)	1(6.8%)	1 (11.1%)	1 (11.1%)	0.507
T1	3 (20.0%)	2 (22.2%)	2(22.2%)	
T2	7 (46.6%)	4 (44.4%)	3 (33.3%)	
T3	4 (26.6%)	2 (22.2%)	3 (33.3%)	
T4				
Histology (%)	2 (13.4%)	4 (44.5%)	1 (11.1%)	0.263
Leiomyosarcoma	7 (46.6%)	2 (22.2%)	2 (22.2%)	
Well differentiated liposarcoma	3 (20.0%)	1 (11.1%)	1 (11.1%)	
Dedifferentiated liposarcoma	3 (20.0%)	2 (22.2%)	5 (55.6%)	
Others				
Compartmental surgery of primary tumor (%)	6 (40.0%)	6 (66.7%)	7(77.8%)	0.157

Others: High grade fibrosarcoma, pleomorphic and high-grade sarcoma

	LR-group(n = 15)	DM-group (n = 9)	LR + DM-group (n = 9)	P value
Time of relapse (months), mean ± SD	38.93 ± 40.49	30.10 ± 25.12	24.44 ± 36.37	0.332
Others: High grade fibrosarcoma, pleomorphic and high-grade sarcoma				

In the LR group, there were 7 cases of well-differentiated liposarcoma (WD-LPS), 3 cases of dedifferentiated liposarcoma (DD-LPS), 2 cases of leiomyosarcoma (LMS) and 3 cases of undifferentiated pleomorphic sarcoma (UPS). In the DM group, there were 2 cases of WD-LPS, 1 case of DD-LPS, 4 cases of LMS, 1 case of UPS sarcoma and 1 case of fibrosarcoma (FS). In the LR + DM group, we included 2 cases of WD-LPS, 1 case of DD-LPS, 1 case of LMS, 3 cases of UPS and 2 cases of high-grade non-specified sarcoma. No significant difference was observed in the mean age, BMI, ASA score, site of the primary RPS, pT stage and histology between the three groups. Similarly, no difference was noted in the rate of compartmental surgery and the interval between primary surgery and first relapse. In Table 2 all the surgical procedures for the recurrence in the three groups were summarized.

Table 2
Surgical procedures

LR-group (n = 15)	
Resection of recurrence	**6**
Resection of recurrence + left hemicolectomy	**2**
Resection of recurrence + left nephrectomy	**1**
Resection of recurrence + right orchifunicolectomy	**1**
Resection of recurrence + ileo-colic resection + omentoplasty + cholecystectomy	**1**
Resection of recurrence + left adrenalectomy	**1**
Resection of recurrence + distal splenopancreasectomy + splenic flexure resection	**1**
Resection of recurrence + perirenal adipose tissue + gonadal vein resections	**1**
Rectal and ileal resection	**1**
DM-group (n = 9)	
Peritoneal recurrence removal + left hemicolectomy	1
Peritoneal recurrence removal + omentectomy	1
Peritoneal recurrence removal + right hemicolectomy	1
Right lung atypical resection	1
Hepatic metastasectomy	2
Hepatic metastasectomy + thermal ablation	3
LR + DM-group (n = 9)	
Resection of local recurrence + ileal resection and hepatic metastasectomy	1
Resection of local recurrence + abdominal wall nodules removal	1
Resection of local recurrencewith left psoas muscle patch + pre-bladder and inguinal nodules	1
Right perirenal recurrence resection + distal pancreatectomy	1
Resection of local recurrenceplus right hemicolectomy and ileum + hepatic metastasectomy	1
Resection of local recurrence + hepatic metastasectomy	1
Resection of local recurrenceplus right hemicolectomy + mesenteric and pre-bladder recurrences resection	1
Left inferior lung atypical resection + abdominal mass resection	1
Resection of local recurrence + splenectomy, diaphragmatic patch and omentectomy for nodules	1

The operative time was significantly lower in the DM group (176.67 ± 72.84 min vs 248.33 ± 92.67 min vs 272.22 ± 56.57, p = 0.03). The rate of positive margin was not statistically different between the three groups (20% in LR group, 11.1% in DM group and 33.3% in LR + DM group; p = 0.079). In 8/15 (53.3%) in the LR group, in 4/9 (44.4%) in the DM group, and in 5/9 (55.5%) in the LR + DM group, the removal of recurrences also required the surgical resection of other organs, p = 0.199. In 5/9 patients of the LR group previously treated with simple RPS removal, surgical resection of the recurrence was associated with total nephrectomy (1 case), left hemicolectomy (2 cases), left adrenalectomy (1 case) and right orchifunicolectomy (1 case). Instead in 3/6 patients in the LR group previously treated with compartmental surgery, one case underwent rectal and ileal resection, one case distal splenopancreasectomy and colic flexure resection, and the remaining one underwent a resection of a previous ileocolic anastomosis, cholecystectomy and duodenal suture with omentoplasty. In the DM group, 6/9 (66.6%) underwent systemic metastasis removal: a lung atypical resection in one case and liver metastasectomy associated with echo-guided thermal ablation in five cases. In the remaining 3/9 (33.4%) peritoneal relapse was associated with omentectomy (1 case), right hemicolectomy (1 case) and left hemicolectomy (1 case). In the LR + DM group, in 7/9 (77.7%) patients the local recurrence was simply removed without organ removal, whereas in 2/9 (22.3%) a right hemicolectomy (1 case) and a left ileo-psoas muscle resection (1 case) was required to achieve negative margins. Systemic metastases were removed in 4/9 cases (44.5%), meanwhile, in 5/9 cases (55.5%) the local recurrence was associated with distant peritoneal nodules removal. No differences were reported in the mean hospital stay between the three groups: 10.8 days for the LR group, 9 days for the DM group and 12.5 days for the LR + DM group, p = 0.332. Similarly, there were no differences in terms of overall complication rate and their severity according to the Clavien-Dindo classification (p = 0.609). No patient was re-operated in the post-operative period in the three groups; only one patient in the LR group died 25 days after the intervention of splenic flexure resection and distal splenopancreatectomy due to sepsis and respiratory distress (Table 3).

Table 3
Perioperative data

	LR-group (n = 15)	DM-group (n = 9)	LR + DM-group (n = 9)	P value
Operative time mean ± SD	248.33 ± 92.67	176.67 ± 72.84	272.22 ± 56.57	**0.034**
Organ resection n (%)	8 (53.3%)	4 (44.4%)	5 (55.5%)	0.104
Positive margin, n (%)	3 (20.0%)	1 (11.1%)	3 (33.3%)	0.079
Hospital stays (days) mean ± SD	10.80 ± 6.44	9.00 ± 3.77	12.56 ± 2.55	0.332
Post-operative complications, n (%)	7 (46.7%)	3 (33.3%)	4 (44.4%)	0.807
Clevien-Dindo, n (%)				0.609
I	2 (28.6%)	0 (0.0%)	2 (50.0%)	
II	2 (28.6%)	2 (66.7%)	2 (50.0%)	
III	2 (28.6%)	1 (33.3%)	0 (0.0%)	
IV	1(14.3%)	0 (0.0%)	0 (0.0%)	
30-days mortality, n (%)	1 (6.6%)	0 (0.0%)	0 (0.0%)	0.996

The mean follow-up was 42.1 months for the LR group, 41.2 months for the DM group and 26.5 months for the LR + DM group (p = 0.277). Ten patients (71.4%) in LR group, six patients (66.7%) in DM group and seven patients (77.8%) in LR + DM group received CT (p = 0.826). The exact CT regimen was not obtainable from all patients, but we could obtain it for 16 patients; half of them received anthracycline-based chemotherapy (2 doxorubicin and dacarbazine; 7 doxorubicin or epirubicin and ifosfamide), 4 patients received trabectedin, while the other received other chemotherapeutic agents (e.g. gemcitabine or taxanes). The second recurrence rate was 78.5% in the LR group, 77.8% in the DM group and 100% in the LR + DM group (p = 0.244). The mean DFS was 24.1 months for the LR group, 26.7 months for the DM group and 12.5 months for the LR + DM group (p = 0.217) (Fig. 1).

Among patients who developed further recurrence, 7/11 (63.6%) patients in the LR group, 2/7 (28.5%) patients in the DM group, and 0/9 (0.0%) patients in the LR + DM group underwent at least one further local treatment of their recurrences (p = 0.010).

In the LR group, all seven cases needed three further treatment sessions of the RPS second to fourth relapses (surgery or percutaneous thermal ablation); one of them also experienced LR plus DM in his course and underwent surgical removal of all nodules. Four patients (57.1%) are still alive after the RPS recurrence surgical removal with a mean follow up of 73 months.

In the DM group, one case underwent removal of a recurrence in the left iliac fossa 25 months after left hemicolectomy for primary mesenteric liposarcoma; subsequently, he underwent left ureteral resection after further 23 months, and he is still alive at a follow up of 75 months. The second patient underwent left inguinal lymphadenectomy plus orchifunicolectomy 12 months after minimally invasive liver metastasectomy for LMS; after that, no other recurrence was detected and he is still alive at 62 months.

In the LR + DM group, no patients underwent further surgical or interventional or procedures, but they were all treated with chemotherapy; only three cases were still alive with a mean follow up of 43 months.

The mean OS was 61.9 months for the LR group, 56.8 months for the DM group and 33.8 months for the LR + DM group ($p = 0.165$) (Fig. 2). In the LR group, the mean OS was 38.0 ± 16.16 months in patients who did not receive chemotherapy and 68.21 ± 10.84 months in patients who were treated with it; in the DM group the mean OS was 47.0 ± 19.79 months and 57.5 ± 12.84 months, respectively; finally, in the LR + DM group, the mean OS was 8.5 ± 0.5 months versus 41.14 ± 9.86 months ($p = 0.05$). Data on follow up are reported in Table 4.

Table 4
Follow-up outcomes

	LR-group (n = 14)	DM-group (n = 9)	LR + DM-group (n = 9)	P value
Follow-up duration (months), mean ± SD	42.14 ± 28.14	41.22 ± 31.62	26.55 ± 22.99	0.277
Peri-operative CT, n (%)	10 (71.4%)	6 (66.7%)	7 (77.8%)	0.826
Second recurrence, n (%)	11 (78.5%)	7 (77.8%)	9 (100.0%)	0.244
LR	9 (81.8%)	1 (14.2%)	0 (0.0%)	
DM	0 (0.0%)	5 (71.6%)	5 (55.6%)	
LR + DM	2 (18.2%)	1 (14.2%)	4 (44.4%)	
Nodule's number, n (%)				0.220
1	4 (36.4%)	1 (14.3%)	0 (0.0%)	
2	2 (18.2%)	0 (0.0%)	1 (11.1%)	
3	2 (18.2%)	2 (28.6%)	2 (22.2%)	
4	2 (18.2%)	2 (28.6%)	0 (0.0%)	
5	1 (9.1%)	1 (14.3%)	0 (0.0%)	
6	0 (0.0%)	0 (0.0%)	2 (22.2%)	
7	0 (0.0%)	1 (14.3%)	1 (11.1%)	
8	0 (0.0%)	0 (0.0%)	1 (11.1%)	
9	0 (0.0%)	0 (0.0%)	2 (22.2%)	
Second recurrence interventional procedures, n (%)	7 (63.6%)	2 (28.6%)	0 (0.0%)	**0.010**
Disease-free survival (months), mean ± SD	24.13 ± 6.05	26.77 ± 9.81	12.55 ± 4.38	0.217
Overall survival (months), mean ± SD	61.99 ± 9.97	56.83 ± 11.44	33.88 ± 8.91	0.165

In all groups, age at the time of RPS recurrence resection, age, sex, ASA score, compartmental surgery of primitive disease, primitive histology, further RPS recurrences and number of nodules, peri-operative CT, and disease-free interval did not represent risk factors for reduced long-term survival both at the univariate and multivariate analysis. Positive resection margins (R1) were correlated with a shorter OS at univariate analysis, whereas further interventional procedures were the only factor that correlated with a shorter OS both at univariate and multivariate analysis (Table 5).

Table 5
Univariate and multivariate analysis for long-term survival

	Univariate Analysis			**Multivariate Analysis**		
	p	HR	95% CI	p	HR	95% CI
Age	0.605	0.990	0.955–1.027			
Sex	0.406	1.566	0.544–4.511			
ASA score	0.253	0.590	0.239–1.457			
Compartmental surgery (%)	0.143	2.302	0.753–7.036			
Histology	0.556	1.162	0.706–1.912			
Margins	**0.017**	**3.882**	**1.279–11.783**	0.225	2.238	0.609–8.233
Peri-operative CT	0.078	0.346	0.106–1.126	0.080	0.268	0.061–1.169
Second recurrence	0.350	32.006	0.022-45774.245			
Nodule's number	0.400	1.127	0.853–1.487			
Second recurrence interventional procedures	**0.014**	**0.063**	**0.007–0.570**	**0.010**	**0.046**	**0.004–0.471**
Disease-Free Interval	0.784	0.998	0.982–1.013			

Discussion

Recurrent RPS disease after curative treatment is associated with a worse prognosis. These patients offer several challenges for surgery, because of the extension or location of the recurrence, but also for the patients' performance status. Furthermore, nowadays the availability of newer medical therapies requires the attentive selection of patients as candidate for surgery, medical therapy or integrated treatments. Some tumoral characteristics determine the pattern of recurrence, as well as the median time of relapse: WD-LPS generally has local recurrences with an indolent behavior over time, whereas LMS tends to have a systemic spread, both early and late in the course of disease [7].

While preliminary works have questioned the role of surgery in locoregional recurrence [8], larger cohort studies [9] have instead demonstrated a significant association between resection and survival in this sub-group of patients. Similarly, Lehnert et al [10] have shown that patients who present with local recurrence from RPS have an increased risk of experiencing further local tumor recurrence, but with a consequent reoperation plan, a respectable long-term survival was achieved. Similarly, in our series LR patients experienced further recurrences, in particular in the original site (81.8% of total). At our centers, a relatively aggressive approach was taken to resect LR by performing a wider excision as it might have

been done for primary RPS. This was in part related to the fact that most primary tumors had been removed in peripheral hospitals, sometimes without compartmental surgery, and only complex cases or recurrences were then referred to our tertiary care institutions. So, our data are in favor of a surgical wide treatment that should be considered when an oncological safe resection could be obtained, even if percutaneous locoregional treatments have been taken into consideration in literature in specifical settings, such as in patients initially unfit for general anesthesia, or to treat single nodules in the retroperitoneal space, such lumbar muscles or iliopsoas one, or parenchymatous organs such as liver [11]. These treatments, were chosen in our series prevalently for further recurrences or combined with surgical resection for the first recurrence.

The management of systemic recurrence is more complex. Although published data are largely retrospective and included heterogeneous populations, there is a consensus to support metachronous metastasectomy [12]. The proper treatment depends on the extension of the disease and should be tailored in a multidisciplinary manner. In our experience, we reported no difference in terms of DFS and OS after surgical resection in the LR versus the DM group with a mean OS of 61.99 and 56.83 months, respectively. This might be related to the fact that up to 66% of the total, distant metastases were usually of limited extension in our series and were treated with parenchymal sparing liver or lung resection (that also can explain the lower operative time for the LR and LR + DM group). The vast majority of patients received CT and three patients, two with LMS and one with DD-LPS, are still alive at a follow up of 84, 62 and 20 months. Indeed, for this specific sub-group, recent clinical literature and systematic review describe long survival, especially when affecting the liver [13]. For these reasons, even if these are metastatic lesions, in selected cases, such as those with an interval between primary surgery and recurrence > 6 months, and small liver lesions, it seems reasonable to take into consideration their surgical resection [14, 15]. Although the literature search did not identify any studies comparing surgery versus chemotherapy in the DM group, a recent study by Smolle et al. [16] compared surgical vs. non-surgical management in a more general cohort of patients with sarcoma lung metastases. This study demonstrated surgery to be associated with significantly longer OS (10-year OS: 23% vs. 4%, $p < 0.001$) and this advantage are independent of baseline characteristics. Moreover, in our opinion, a radical approach should be taken into consideration also in the case of resectable DM after previous surgery for recurrent disease [17], because it could influence positively the OS, as we reported from our experience in which repeated interventional procedures is the leading factor both at univariate and multivariate analysis.

The present work describes one of the highest percentages of repeated surgery for RPS recurrence, as we described "re-do" surgery in 50% of patients who presented new resectable recurrences after the surgical treatment of the first RPS recurrence, with a percentage of 63% in LR group (also in case of distant spread in one patient), and 28% in DM group. Instead, for the LR + DM group albeit all cases experience new recurrence, no one was reoperated. This is in line with the trans-Atlantic RPS Working group consensus document [13] that state that surgery has a more limited role in patients with liver disease associated with an extra-liver disease or multifocal abdominal metastases. However, all these patients were operated on for the first recurrence with complete resection of all nodules/metastasectomy. To date, very scarce

literature is present on the surgical treatment of both local and metastatic RPS recurrences, in particular with multiple peritoneal implants or systemic spread. This aspect could be considered another key point of our analysis, although on a limited number of patients, and it seems to support the possibility of a surgical approach in case of RPS recurrences, also in patients with LR + DR, as we obtained satisfactory short-term and long-term results compared to other studies on this argument [17].

In the LR + DR group, 33.3% of patients had positive margins at the final histological report, but this may be due to the fact the large masses had been removed. Margin resection is a risk factor that increased mortality in univariate analysis, but not in multivariate one. However, the question of positive margins is still very debated. Even if different investigators found no benefit for tumor incomplete resection compared to exploration alone [18], a recent study addressed the question of clinical outcome in patients with retroperitoneal LPS, focusing on positive margins and surgical debulking [19]. These authors found a survival benefit in patients after incomplete resection with a median survival of 26 months compared to exploration alone with a median survival of 4 months. A meta-analysis of patients undergoing incomplete resection of RPS found an improvement in survival time after cytoreductive tumor resection [20]. We can then say that even if a good pre-operative evaluation is mandatory to offer surgical resection to those patients who are very likely to achieve an R0-resection, in those cases who achieved an R1 resection there might still be some benefit deriving from surgery, even if in these cases the integration with radiotherapy or medical therapy becomes fundamental.

Our study has some limitations due to its retrospective nature. First of all, a possible selection bias could be present. An unknown percentage of patients with resectable recurrences was probably treated only by the oncologist without a surgical evaluation. Moreover, we included patients enrolled in a long period in which medical therapies have undergone important improvements and nowadays we have various valid treatment options with different impacts in terms of cancer-specific and overall survival. Furthermore, although all patients have been always followed by oncologists after surgery (even in different centers and regions), we were not able to collect detailed information about the medical therapy regimen they underwent after the surgical operation, and therefore we were not able to report detailed information about these data. Furthermore, local treatment such as percutaneous thermal ablation might have a role but no randomized studies compare the efficacy of surgical procedures versus the only medical therapy versus these treatments. Concerning systemic therapy, there is not enough evidence to use post-operative therapy after surgical recurrence resection [12]. Medical therapy, on the other hand, could play a role before interventional procedures to downsize the recurrence, especially locoregional ones. Finally, the small sample size, particularly in the DM group and LR + DM group, limits a reliable statistical analysis.

To conclude, data emerged from the present series suggested additional information to the RPS recurrence scenario and should encourage a thorough multidisciplinary evaluation of patients with recurrent RPS performed by general surgeons, interventional radiologists, and oncologists to take into consideration a possible surgical treatment of the RPS recurrences, also in patients who have already undergone surgical resection of RPS recurrence and developed new treatable RPS recurrences during the follow-up. Although no differences in terms of DFS and OS between our three groups were detected, the

importance of repeated interventional procedures seems to be particularly important in the LR group and DM group. Locally directed therapy, such as surgical and ablative approaches, may be integrated and can offer a potentially long survival in selected patients. Therefore, even in those cases in which RPS recurrence is located in the liver or lung, when an R0 resection could be obtainable, surgical resection could be taken into consideration, especially in high volume surgical centers, because surgical resection has been demonstrated to have a positive impact on long-term oncological results. LR + DM group is the worst survival group in which no further interventional maneuvers were taken into consideration as the progression of intra-abdominal disease; however, the DFS and OS seem to be reliable compared to other works in which the LR + DM relapse was not removed supporting the importance of surgery also in this setting with related low morbidity. Probably, a combination of therapies and progress in the management will be crucial for this kind of patient in the future. However, given the rarity of this pathology and particularly for the resectable RPS metastases, this arena would benefit from prospective multi-institutional collaborative efforts to define the role of peri-operative chemotherapy as adjuncts to surgical excision and percutaneous ablation and to delineate the optimum sequences of these therapies in the treatment of these patients as well as a detailed risk evaluation for survival.

Declarations

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Conflict of interest: the authors declare that they have no conflict of interest.

Ethical standard: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

Authors' Contributions: *Study conception and design:* Guadagni Simone, Peri Andrea, Palmeri Matteo, Morelli Luca; *Acquisition of data:* Guadagni Simone, Peri Andrea, Mercine Chiara, Filardo Matteo, Palmeri Matteo, Bianchini Matteo, Comandatore Annalisa, Guadagni Simone, Furbetta Niccolò, Sbrana Andrea, Pollina Luca Emanuele, Gaeta Raffaele; *Analysis and interpretation of data:* Guadagni Simone, Pietrabissa Andrea, Galli Luca, Di Candio Giulio, Morelli Luca, Di Franco Gregorio; *Drafting of manuscript:* Guadagni Simone, Sbrana Andrea, Morelli Luca; *Critical revision of manuscript:* Guadagni Simone, Morelli Luca, Peri Andrea, Pietrabissa Andrea, Di Candio Giulio; *Study Final approval:* Guadagni Simone, Di Franco Gregorio, Morelli Luca

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Figures

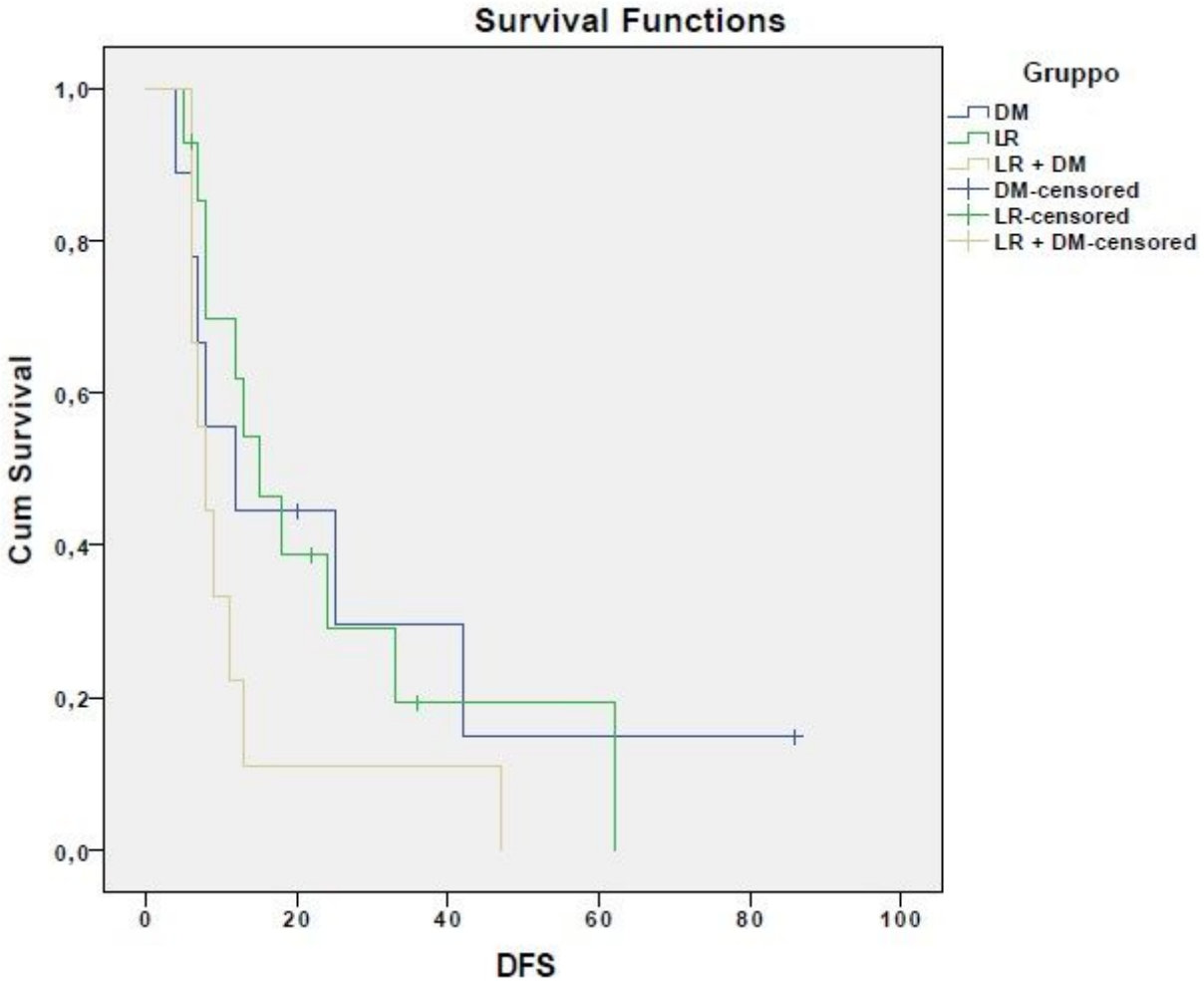

Figure 1

Disease-free survival in the three groups

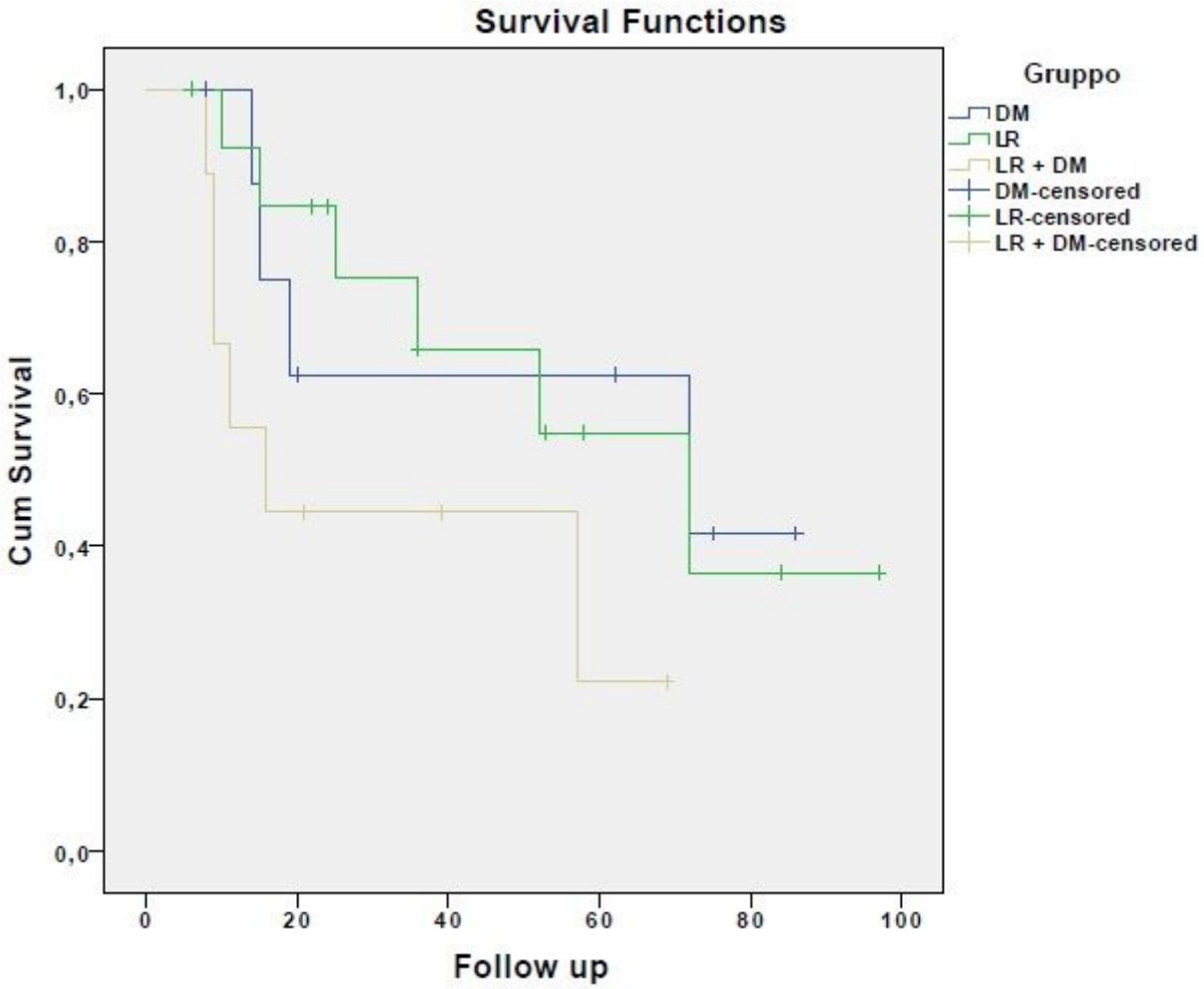

Figure 2

Overall survival in the three groups