



## Intraperitoneal Invasion of Retroperitoneal Sarcomas: A Risk Factor for Dismal Prognosis

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### ABSTRACT

**Introduction.** Retroperitoneal sarcomas (RPS) lie in the retroperitoneal space and are covered by a peritoneal layer. However, some RPS have an intraperitoneal component (IPC), which invades into the peritoneal cavity. The significance of such a clinical presentation is unknown.

**Methods.** We retrospectively analyzed our prospectively maintained institutional database of RPS, along with intraoperative photographs taken to document the primary tumor extent at laparotomy. The effects of IPC on overall survival (OS), local recurrence (LR), and distant metastasis (DM) were evaluated.

**Results.** IPC was present in 81 of 493 patients (16.4%). It was significantly associated with older age (64 vs. 59,  $p = 0.008$ ), gender (67% vs. 33% males,  $p = 0.005$ ), and multifocality (11.1% vs. 0.5%;  $p < 0.0001$ ). IPC was not associated with size or any specific histology, while it showed a weak association with high malignancy grade (40.7% vs. 28.6% in G3 tumors;  $p = 0.076$ ). At a median follow-up of 32 months IPC was associated with worse 5-year OS (54% vs. 74%,  $p < 0.001$ ) and crude cumulative incidence (CCI) of LR (5-year CCI of LR: 38% vs. 19%,

$p = 0.001$ ), but not to CCI of DM. However, multivariable models showed that IPC's effect on OS (HR: 1.52, 95% CI 0.92–2.49,  $p = 0.1$ ) and LR (HR: 1.34, 95% CI 0.8–2.26,  $p = 0.27$ ) could be sufficiently explained by other known risk factors.

**Conclusions.** IPC is associated with increased LR and decreased survival. However, the effect of IPC on prognosis is predominantly related to other tumor characteristics already included in published nomograms. IPC should not be a contraindication to a proper surgical resection.

Retroperitoneal sarcomas (RPS) are histologically heterogeneous group of mesenchymal tumors.<sup>1</sup> As implied by their name, the tumors are located in the retroperitoneum and hence are usually covered by a thin peritoneal layer or by other organs. Surgery is the only curative options for these tumors, and it commonly mandates multivisceral resections to excise the tumor completely while covered by normal tissue.<sup>2,3</sup> However, even after adequate surgery, prognosis is variable and depends on multiple factors.<sup>4</sup> Research conducted in recent years highlighted different prognostic factors, such as age, tumor size, histological subtype, grade, multifocality, and completeness of surgical resection.<sup>5,6</sup> These prognostic factors have been incorporated into a well-validated nomogram and enable patient-specific prognostication.<sup>7</sup> The ability to

predict risk of recurrence or death can be factored into treatment decision (such as addition of adjuvant treatment) and patient counseling.<sup>8</sup>

It is known that multifocal presentation of RPS, i.e., having more than one noncontiguous tumor, is associated with worse oncological outcomes.<sup>7,9</sup> However, sometimes RPS present with an intraperitoneal component (IPC), i.e., part of the tumor is not covered by peritoneum or other organs and hence is intraperitoneal. The IPC can be either adherent to the main tumor mass or not. Thus, the concept of multifocality does not specifically address tumor relation with the peritoneum, although multifocality may be associated with IPC. Tumor ability to invade into the peritoneal layer may attest to its aggressiveness and may affect its tendency to intra-abdominal recurrence. However, the significance of this presentation in terms of association with other clinical parameters or oncological outcomes is not reported. Beside prognostic information, this also may inform intraoperative decision on the extent of surgical resection. The purpose of this study was to compare clinical presentation and oncological outcomes of tumors with IPC to tumors that are completely retroperitoneal.

## PATIENTS AND METHODS

### *Patients and Treatment*

Patients who underwent surgery for primary RPS between January 2005 and November 2017 were identified from a prospectively maintained institutional database ( $n = 500$ ), which contained also photographs taken at the beginning of the operation, after laparotomy. These pictures allowed us to identify tumors with IPC. A tumor was considered to have an IPC if it had a component that penetrates the peritoneum, whether contiguous with the main tumor mass or not. Tumors could have both IPC and multifocality. For the purpose of this study, visceral sarcomas (i.e., gastrointestinal tract or genitourinary tract), gastrointestinal stromal tumors, as well as desmoid tumors and pediatric sarcomas (i.e., primitive Peripheral Neuro-Ectodermal Tumor (pPNET)/extraosseous Ewing sarcoma, embryonal/alveolar rhabdomyosarcoma, desmoplastic small round cell tumor) were excluded. We excluded 7 patients with missing values of the main prognostic variables, i.e., IPC (5 pts), grade (1 pt), and size (1 pt); thus, the analysis set included 493 pts. All patients were uniformly treated by primary extended resection, which was classified as macroscopically complete (R0 or R1) or incomplete (R2). Grade was determined according to the FNCLCC grading system.<sup>10</sup> Neoadjuvant chemotherapy (CT) was provided according to standard regimens used at the time or within institutional/multi-institutional clinical trials.

When delivered, radiotherapy (RT) was provided through external beams at doses ranging from 36 to 65 Gy (median 50 Gy). Patients were operated on 4–6 weeks after completion of preoperative treatment. Patients were prospectively followed by CT scan of chest and abdomen every 4 months for the first 2 years, then every 6 months for the following 3 years, and yearly thereafter. The study was approved by the institutional review board.

### *Statistical Analysis*

Median and interquartile range extremes (IQRE) were used to describe continuous variables, whereas categorical variables were expressed as absolute and relative frequency according to IPC and compared by means of Wilcoxon rank-sum test or Fisher's exact test. Overall survival (OS) was defined as the time between surgery and death from any cause; time was censored at the date of last follow-up for patients remaining alive. Survival curves were estimated with the Kaplan–Meier method and compared by the log-rank test. Multivariable analysis for OS was performed by the Cox proportional hazards regression model. Crude cumulative incidence (CCI) for local recurrence (LR) and distant metastasis (DM) were estimated, and multivariable analyses were performed by means of Fine and Gray models. The analyses were performed in a competing risks framework.<sup>11</sup> For LR (DM), deaths without evidence of disease and DM (LR) were regarded as competing events.

Concomitant LRs and DMs were considered DM. In all models, the categorical variables were modelled using dummy variables, and the continuous variables were modelled using three-knot restricted cubic splines.<sup>12</sup>

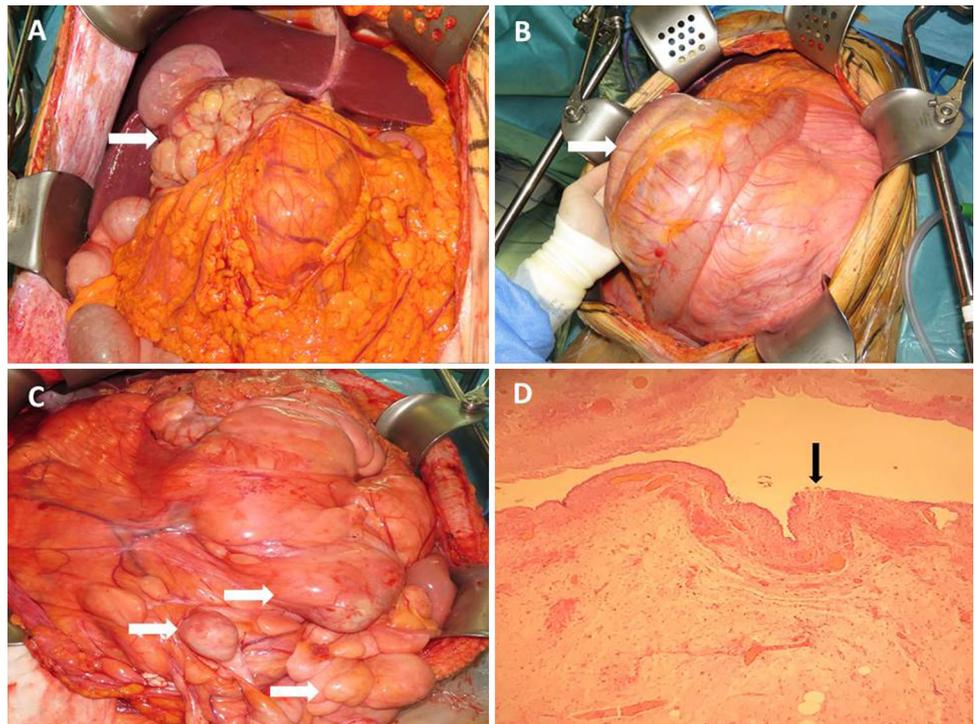
All statistical analyses were performed using SPSS for Windows version 25 (SPSS, Munich, Germany) and R software (<http://www.r-project.org/>).  $p < 0.05$  was considered significant.

## RESULTS

We included 493 patients in this analysis; 81 of them had an IPC. Figure 1A shows a typical RPS classified as IPC tumor. Figure 1B shows another tumor classified as IPC, whereas in Fig. 1C a tumor with both IPC and multifocality is shown. Figure 1D shows that in accordance with the macroscopic appearance, these tumors lack an overlying peritoneal layer.

Table 1 shows the demographic and clinic-pathological characteristics of patients according to IPC. IPC is significantly more common in males (66.7% vs. 49.1%;  $p = 0.005$ ) and in the older age (64 vs. 59;  $p = 0.008$ ). IPC was not associated with a specific sarcoma histological subtype, whereas it showed a weak association with higher

**FIG. 1** Clinical presentation of retroperitoneal sarcoma (RPS) with intraperitoneal component (IPC). **A, B** RPS + IPC in photographs taken after laparotomy. White arrows mark the IPC. **C** Multifocal RPS with several IPCs (marked by white arrow). **D** Histological section of a RPS with IPC black arrow marks the transition between the component covered with peritoneum (to the left of the arrow) and IPC (to the right of the arrow)  $\times 10$



grade ( $p = 0.076$ ). The presence of IPC was significantly associated with multifocality (11% vs. 0.5%,  $p < 0.001$ ), although the majority of the IPC cases had unifocal disease. In addition, the presence of IPC was significantly associated with macroscopically incomplete resection (7.4% vs. 1.2%;  $p = 0.004$ ). The use of perioperative chemotherapy or neoadjuvant radiotherapy did not differ between the two groups of patients.

#### Effects of Intraperitoneal Invasion on OS

After a median follow-up of 32 months, 1-, 3-, and 5-year OS (95% confidence interval [CI]) was 94% (91.7–96.5), 81% (76.3–85.2), and 74% (68.1–79.4) for patients without IPC versus 86% (78.7–94.1), 66% (55–80.4), and 54% (39.9–73.6) for patients with IPC (Fig. 2). Multivariable analysis that included other known risk factors showed that beside age (HR = 1.55, 95% CI 1.10–2.19;  $p = 0.037$ ), tumor grade (HR = 8.88, 95% CI 1.92–41.92 for G2 vs. G1; HR = 26.68, 95% CI 5.65–125.86 for G3 vs. G1,  $p < 0.0001$ ), and complete macroscopic resection were significant predictors for OS. IPC showed a trend for significance (HR = 1.52, 95% CI 0.92–2.49,  $p = 0.1$ ; Table 2).

#### Patterns of Recurrence Associated with Intraperitoneal Invasion of RPS

We hypothesized that IPC would be associated with increased local intra-abdominal recurrence due to the ability of tumor cells to spread in the abdominal cavity. Figure 3 compares CCI of LR between the two patient groups. Patients without IPC had 1-, 3-, and 5 years CCI (95% CI) of LR rates of 8.5% (6–11%), 16% (12–20%), 19% (16–25%), respectively, whereas patients with IPC had 19% (12–30%), 27% (18–39%), 38% (27–53%), respectively ( $p = 0.001$ ). Multivariable analysis (Table 2) showed that tumor size (HR = 1.33, 95% CI 0.82–2.16;  $p = 0.034$ ), grade (HR = 3.99, 95% CI 1.33–12.01 for G2 vs. G1; HR = 6.00, 95% CI 2.06–17.52 for G3 vs. G1,  $p = 0.002$ ) and histology subtype (HR = 0.42, 95% CI 0.14–1.29 for DD LPS vs. WD LPS; HR = 0.06, 95% CI 0.01–0.28 for LMS vs. WD LPS,  $p = 0.003$ ) were significant predictors of LR. IPC's effect on LR (HR 1.34, 95% CI 0.80–2.26,  $p = 0.268$ ) was sufficiently explained by other risk factors.

CCI of DM showed no difference between the two patient groups (Fig. 3): 1-, 3-, and 5-year CCI (95% CI) were 8% (6–11%), 12% (9–16%), 16% (12–20%), respectively for patients with no IPC versus 8% (4–18%), 8% (4–18%), and 16% (8–29%) for those with IPC ( $p = 0.63$ ; Fig. 4).

**TABLE 1** Demographic and clinicopathological characteristics of the cohort

	Retroperitoneal n (%)	Intraperitoneal component n (%)	<i>p</i>
Overall	412 (83.6)	81 (16.4)	
Gender			0.005
Female	209 (50.9)	27 (33.3)	
Male	202 (49.1)	54 (66.7)	
Age (year)			0.008
Median (IQRE)	59 (49–68)	64 (55–70)	
Tumor size (cm)			0.001
Median (IQRE)	20 (12–27)	21 (17–35)	
Histological subtype			0.290
WD LPS	94 (22.8)	19 (23.5)	
DD LPS	155 (37.6)	39 (48.1)	
LMS	69 (16.7)	13 (16.0)	
SFT	31 (7.5)	3 (3.7)	
MPNST	13 (3.2)	2 (2.5)	
UPS	7 (1.7)	2 (2.5)	
Other	43 (10.4)	3 (3.7)	
FNCLCC grade			0.076
I	142 (34.5)	20 (24.7)	
II	152 (36.9)	28 (34.6)	
III	118 (28.6)	33 (40.7)	
Multifocality			< 0.001
Yes	2 (0.5)	9 (11.1)	
No	410 (99.5)	72 (88.9)	
Completeness of surgical resection			0.004
R0/R1	407 (98.8)	75 (92.6)	
R2	5 (1.2)	6 (7.4)	
Chemotherapy			0.381
Yes	88 (21.4)	21 (25.9)	
No	324 (78.6)	60 (74.1)	
Radiotherapy			0.745
Yes	70 (17.0)	12 (14.8)	
No	342 (83.0)	69 (85.2)	

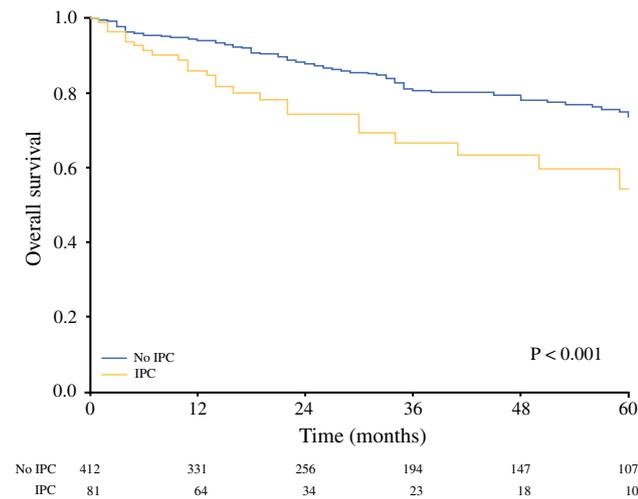
*IQRE* interquartile range extremes, *FNCLCC* Federation Nationale des Centres de Lutte Contre le Cancer, *LMS* leiomyosarcoma, *DD* dedifferentiated, *WD* well-differentiated, *LPS* liposarcoma, *MPNST* malignant peripheral nerve sheath tumor, *SFT* solitary fibrous tumor, *UPS* undifferentiated pleomorphic sarcoma, *R0* macroscopically complete resection with negative microscopic margins, *R1* macroscopically complete resection with positive microscopic margins, *R2* macroscopically incomplete resection

## DISCUSSION

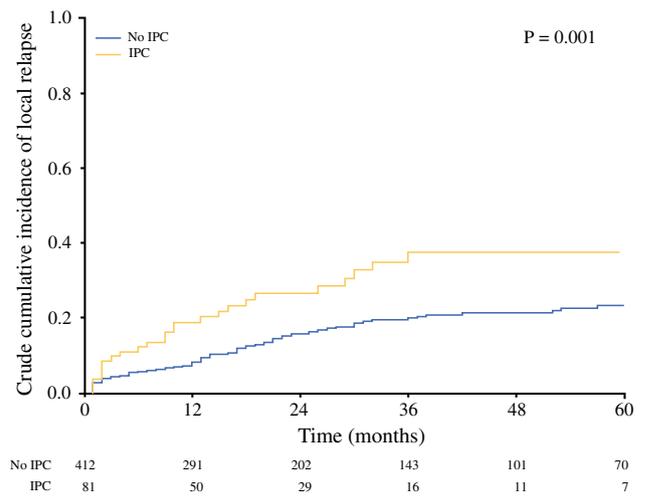
In this series of 493 patients affected by primary RPS, surgically treated at a single institution during a 12-year time span, IPC occurred in 16% of the cases without an independent association to a higher risk of LR or death. After proper management, half of the patients with intra-operative findings of IPC were alive and free of disease at 5 years.

Our hypothesis was that the ability of the tumor to invade through the peritoneal layer could represent increased tumor aggressiveness, which would be finally manifested as increased risk for LR and decreased OS.<sup>13,14</sup> However, this association was not independent. IPC did not increase per se LR or decrease OS.

Theoretically, a higher LR incidence should demand a wider resection margin, as previously implied for specific RPS histological subtypes.<sup>4,15</sup> However, in a setting where a wider resection margin cannot be obtained because of the intra-abdominal invasion of the disease, one could favor a



**FIG. 2** Overall survival curves according to intraperitoneal component



**FIG. 3** Crude cumulative incidence of local recurrence according to intraperitoneal component

**TABLE 2** Results from the multivariable Cox/Fine and Gray models for overall survival and local recurrence

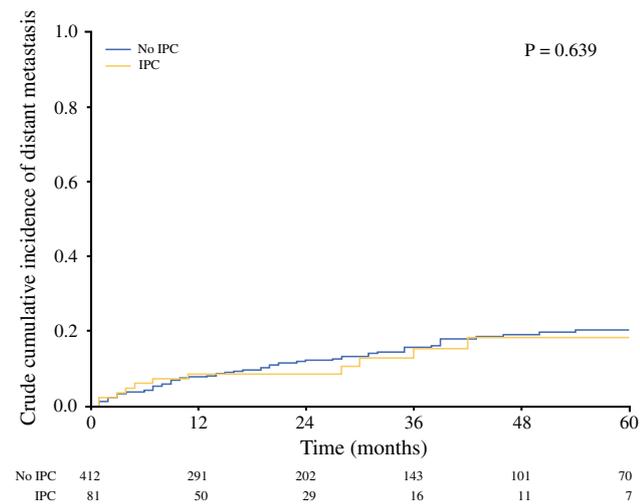
	Overall survival			Local recurrence		
	HR	95% CI	<i>p</i>	HR*	95% CI	<i>p</i>
Age (year)			0.037			0.231
69 versus 50**	1.55	1.10–2.19		1.31	0.94–1.83	
Tumor size (cm)			0.720			0.034
28 versus 13**	1.15	0.73–1.80		1.33	0.82–2.16	
Completeness of resection			< 0.001			0.515
R2 versus R0/R1	6.70	2.89–15.50		1.56	0.41–5.87	
Multifocality			0.353			0.675
Yes versus no	1.61	0.59–4.39		1.26	0.43–3.72	
Histologic subtype			0.381			0.003
DD LPS versus WD LPS	0.46	0.10–2.16		0.42	0.14–1.29	
LMS versus WD LPS	0.33	0.06–1.79		0.06	0.01–0.28	
MPNST versus WD LPS	0.30	0.04–2.16		–	–	
SFT versus WD LPS	0.35	0.06–2.03		–	–	
UPS versus WD LPS	0.92	0.16–5.47		–	–	
Other*** versus WD LPS	0.61	0.12–3.19		0.34	0.12–0.99	
FNCLCC grade			< 0.001			0.002
II versus I	8.88	1.92–41.21		3.99	1.33–12.01	
III versus I	26.68	5.65–125.86		6.00	2.06–17.52	
Intraperitoneal component			0.100			0.268
Yes versus no	1.52	0.92–2.49		1.34	0.80–2.26	
Chemotherapy			0.398			0.039
Yes versus no	1.23	0.76–2.01		1.66	1.03–2.70	
Radiotherapy			0.521			0.694
Yes versus no	1.18	0.71–1.94		0.89	0.51–1.56	

HR hazard ratio, CI confidence interval, *P* two-sided Wald test *p* value, FNCLCC French National Federation of the Centers for the Fight Against Cancer, DD LPS dedifferentiated liposarcoma, WD LPS well-differentiated liposarcoma, LMS leiomyosarcoma

\*Subdistribution hazard ratios

\*\*Third versus first quartile

\*\*\*Including MPNST, SFT, and UPS histology



**FIG. 4** Crude cumulative incidence of distant metastases according to intraperitoneal component

more conservative approach, because the LR risk would be high anyway. However, this did not prove to be the case, and more than 50% of the patients with IPC were alive and disease free at 5 years. Therefore, the finding of an IPC at laparotomy should not be an argument for a more limited resection. On the other hand, IPC could demand the addition of locoregional treatment because of this increased LR incidence—a suggestion that should be explored in future studies.<sup>16,17</sup>

The presence of IPC is more common in males and in older age. Age is a well-recognized risk factor for RPS outcome and was incorporated into validated nomograms.<sup>7,8</sup> Although IPC was not associated with a specific histological subtype, it occurred more often in higher grade tumors. In general, grade reflects the ability of sarcoma to metastasize and also is associated with higher death risk. The presence of IPC was associated with multifocality and incomplete surgical resection. Indeed, these features are associated with a locally advanced disease, and it is therefore logical that invasion of the peritoneum may be present in these cases. In addition, multifocality and incomplete resection per se have negative impact on prognosis, which the IPC does not significantly modify.

Another example of the biological aggressiveness implied by tumor natural barrier invasion was recently described. Retrospective analysis of histologic organ invasion (HOI) showed that it was independently associated with an increased DM risk and statistically significant worse OS.<sup>18</sup> On the contrary, IPC was not associated with increased metastatic risk. Given the retrospective nature of our analysis, we could not reliably assess the frequency of HOI, so it is difficult to assess the relationship between these two tumor features. However, they seem to be different as a clear association with a higher metastatic

incidence in IPC was not found. Thus, while IPC is a clinical presentation associated with increased LR incidence, HOI is associated with an increased DM incidence. Interestingly, there seem to be two separate groups of grade 3 de-differentiated liposarcoma (DDLPS)—one more prone to DM recurrence and one more prone to LR—similar to other LPS subtypes but with shorter disease-free interval.<sup>19</sup> IPC appears strongly associated with the high-grade DDLPS more prone to LR, predicting this pattern of failure.

Our study has several limitations. We did not find any predictor of IPC on preoperative imaging. Even multifocal tumors were found to be completely retroperitoneal as shown in Table 1. IPC was predominantly identified by photographs taken at the beginning of the operation. These photographs were systematically performed in all patients since January 2005. This was not paired to a systematic pathological analysis of the peritoneal surface. However, because IPC is predominantly an intraoperative finding, a pathological assessment cannot be performed in real time. It is possible that the presence of tumor cells in cytological analysis of peritoneal fluid may be a better predictor for LR, which could serve as a marker for the need of regional treatment. However, in the absence of routine cytological analysis of peritoneal lavage, this assumption is highly speculative.

In conclusion, while IPC was associated to other well-known higher risk factors, such as grade and multifocality, it did not independently predict the outcome. These findings should be of help in the complex intraoperative decision making for the proper management of these diseases.

**DISCLOSURE** The authors have nothing to disclose.

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