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Morbidity and Outcomes After Distal Pancreatectomy for Primary Retroperitoneal Sarcoma: An Analysis by the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group

Sanjay P. Bagaria, MD[1], Carol Swallow, MD[2], Harini Suraweera, MS[2], Chandrajit P. Raut, MD[3], Mark Fairweather, MD[3], Ferdinando Cananzi, MD[4,5], Vittorio Quagliuolo, MD[4,5], Giovanni Grignani, MD[6], Daphne Hompes, MD[7], Samuel J. Ford, MD[8], Carolyn Nessim, MD[9], Sameer Apte, MD[9], Jacek Skoczylas, MD[10], Piotr Rutkowski, MD[10], Sylvie Bonvalot, MD[11], Dimitri Tzanis, MD[11], Emmanuel Gabriel, MD[1], Elisabetta Pennacchioli, MD[12], Markus Albertsmeier, MD[13], Robert J. Canter, MD[14], Raphael Pollock, MD[15], Valerie Grignol, MD[15], Kenneth Cardona, MD[16], Adriana C. Gamboa, MD[16], Marko Novak, MD[17], Eberhard Stoeckle, MD[18], Martin Almquist, MD[19], Nita Ahuja, MD[20], Nicholas Klemen, MD[20], Winan Van Houdt, MD[21], David Gyorki, MD[22], Alexandra Gangi, MD[23], Marco Rastrelli, MD[24], Jos van der Hage, MD[25], Yvonne Schrage, MD[25], Sergio Valeri, MD[26], Lorenzo Conti, MD[27], Matthew R. Spiegel, BS[1], Zhou Li, MS[1], Marco Fiore, MD[27], and Alessandro Gronchi, MD[27]

[1]Department of Surgery, Mayo Clinic, Jacksonville, FL; [2]Department of Surgery, Mount Sinai Hospital and Princess Margaret Cancer Center, Toronto, Canada; [3]Division of Surgical Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA; [4]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [5]Sarcoma, Melanoma and Rare Tumors Surgery Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [6]Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy; [7]Department of Surgical Oncology, University Hospitals Gasthuisberg, Leuven, Belgium; [8]Department of Surgery, University Hospitals Birmingham, Birmingham, UK; [9]Department of Surgery, University of Ottawa, Ottawa, Canada; [10]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [11]Department of Surgery, Institut Curie, Paris, France; [12]Division of Melanoma, Sarcomas and Rare Tumors, IEO, European Institute of Oncology, IRCCS, Milan, Italy; [13]Department of General, Visceral, and Transplantation Surgery, Ludwig Maximilians Universitat Munich, Munich, Germany; [14]Department of Surgery, University of California-Davis School of Medicine, Sacramento, CA; [15]Division of Surgical Oncology, The Ohio State University, Columbus, OH; [16]Division of Surgical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; [17]Department of Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia; [18]Department of Surgery, Institut Bergonie, Bordeaux, France; [19]Department of Surgery, Skane University Hospital, Lund University, Lund, Sweden; [20]Department of Surgery, Smilow Cancer Institute, Yale University School of Medicine, New Haven, CT; [21]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; [23]Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia; [22]Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA; [24]Department of Surgical Oncology, Veneto Institute of Oncology, Padua, Italy; [25]Department of Surgery, Leiden University Medical Center, Leiden, Netherlands; [26]Department of Surgery, Campus Bio-Medico, Rome, Italy; [27]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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S. P. Bagaria, MD
e-mail: bagaria.sanjay@mayo.edu

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ABSTRACT

Background. Multi-visceral resection often is used in the treatment of retroperitoneal sarcoma (RPS). The morbidity after distal pancreatectomy for primary pancreatic cancer is well-documented, but the outcomes after distal pancreatectomy for primary RPS are not. This study aimed to evaluate morbidity and oncologic outcomes after distal pancreatectomy for primary RPS.

Methods. In this study, 26 sarcoma centers that are members of the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) retrospectively identified consecutive patients who underwent distal pancreatectomy for primary RPS from 2008 to 2017. The outcomes measured were 90-day severe complications (Clavien-Dindo $\geq$ 3), postoperative pancreatic fistula (POPF) rate, and oncologic outcomes.

Results. Between 2008 and 2017, 280 patients underwent distal pancreatectomy for primary RPS. The median tumor size was 25 cm, and the median number of organs resected, including the pancreas, was three. In 96% of the operations, R0/R1 resection was achieved. The 90-day severe complication rate was 40 %. The grades B and C POPF complication rates were respectively 19% and 5% and not associated with worse overall survival. Administration of preoperative radiation and factors to mitigate POPF did not have an impact on the risk for the development of a POPF. The RPS invaded the pancreas in 38% of the patients, and local recurrence was doubled for the patients who had a microscopic, positive pancreas margin (hazard ratio, 2.0; $p = 0.042$).

Conclusion. Distal pancreatectomy for primary RPS has acceptable morbidity and oncologic outcomes and is a reasonable approach to facilitate complete tumor resection.

Retroperitoneal sarcoma (RPS) is a rare tumor that can often reach massive size before detection. En bloc resection is the cornerstone in the management of non-metastatic primary RPS. Resections can be challenging due to large tumor size and possible involvement of neighboring organs. Not uncommonly, RPS operations involve multi-visceral resections. As a result, the decision to resect organs is based on the balance between obtaining optimal oncologic disease control and at the same time avoiding severe complications.

Distal pancreatectomy is most frequently performed for primary neoplasms of the pancreas. In the setting of RPS, it is performed for left-sided RPS that either invades or abuts the distal pancreas. Complications, including postoperative pancreatic fistula (POPF), are well-documented for primary pancreatic disease,[1–4] but whether distal pancreatectomy in the setting of RPS has similar or worse outcomes is not known.

The Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) is a multi-institutional, international collaboration dedicated to improving our understanding and the treatment of RPS. The group has published several studies and consensus guidelines.[5–11]

In this study, TARPSWG retrospectively identified primary RPS patients for whom distal pancreatectomy was performed. The primary objective was to determine the postoperative morbidity after distal pancreatectomy for primary RPS. The secondary objectives were to determine whether POPF affects long-term oncologic outcomes and how often the pancreas is invaded by RPS.

METHODS

Patients were enrolled in this study from 26 member institutions (Table 1). The inclusion criteria specified a diagnosis of primary RPS for which distal pancreatectomy was performed between 1 January 2008 and 31 December and an age greater than 18 years. The exclusion criteria ruled out patients with a follow-up period shorter than 30 days (unless they died within 30 days), recurrent RPS, pelvic sarcomas, and any of the following histologic subtypes: desmoid tumors, gastrointestinal stromal tumors, Ewing sarcoma, peripheral neuroectodermal tumor, desmoplastic small round cell tumor, embryonal/alveolar rhabdomyosarcoma, and uterine sarcoma. Institutional review board approval was obtained at each institution.

In this study, POPF was defined according to the updated 2016 International Study Group Pancreatic Fistula consensus guidelines.[12] In brief, POPF grade A is characterized as a biochemical leak and not considered a true pancreatic fistula, whereas POPF grade B comprises a fistula that requires invasive procedures to manage, and grade C comprises a fistula that results in organ failure, reoperation, and/or death.

The occurrence and severity of POPF grades B and C were calculated through 90 days after the index operation. Other postoperative complications were scored based on the Clavien-Dindo scoring system. There was no centralized review of the pathology. Pathology reports were reviewed for evidence of pancreatic invasion, defined as invasion into the pancreas parenchyma, peripancreatic tissue, or both.

Continuous variables were summarized as mean $\pm$ standard deviation) and as median (range), whereas categorical variables were reported as frequency (percentage).

TABLE 1 Participating institutions

Institution	Distal pancreatectomy *n* (%)	Left-sided RPS *n* (%)
Campus Bio-Medico Rome	1 (0.4)	5 (0.4)
Candiolo Cancer Institute IRCCS	13 (4.6)	63 (5.5)
Cedars Sinai Medical Center	2 (0.7)	12 (1.0)
Dana Farber Cancer Institute	22 (7.8)	57 (4.9)
Emory University	5 (1.8)	9 (0.8)
Fondazione IRCCS Istituto Nazionale dei Tumori	93 (32.9)	181 (15.7)
Humanitas University	17 (6.0)	53 (4.6)
IEO European Institute of Oncology	7 (2.5)	17 (1.4)
Institut Bergonié	5 (1.8)	46 (4.0)
Institut Curie-Paris	8 (2.8)	57 (4.9)
Institute of Oncology Ljubljana	5 (1.8)	16 (1.4)
Leiden University Medical Center	1 (0.4)	17 (1.5)
Ludwig Maximilians Universitat	7 (2.5)	24 (2.1)
Lund University Hospital	4 (1.4)	34 (2.9)
Maria Sklodowska-Curie National Research Institute	8 (2.8)	33 (2.9)
Mayo Clinic	7 (2.5)	41 (3.6)
Mount Sinai Hospital and Princess Margaret Cancer Center	23 (8.1)	159 (13.8)
Netherlands Cancer Institute	3 (1.1)	34 (2.9)
Ohio State University	6 (2.1)	41 (3.6)
Peter MacCullum Cancer Center	3 (1.1)	6 (0.5)
University of California-Davis	6 (2.1)	31 (2.7)
University Hospital Birmingham	9 (3.2)	67 (5.8)
University Hospitals Gasthuisberg Leuven	11 (3.9)	53 (4.6)
University of Ottawa	9 (3.2)	33 (2.9)
Veneto Institute of Oncology	2 (0.7)	13 (1.1)
Yale University	3 (1.1)	8 (0.7)
Total	280	1114

RPS, retroperitoneal sarcoma

The association between risk factors and overall 90-day Clavien-Dindo complication rates were tested using the Wilcoxon rank-sum test for continuous risk factors and the chi-square test for categorical risk factors. Univariable logistic regression was used to identify significant risk factors and to estimate the odds ratios for the development of 90-day Clavien-Dindo complication and grades B and C POPF.

Uni- and multivariable Cox regression models were used to identify variables associated with local recurrence, distant recurrence, and overall mortality starting 90 days after surgery. A multivariable Cox regression model for each outcome included all predictors that were significant in the univariable analysis for that outcome. All tests were two-sided, with the alpha level set at 0.05. The analysis was performed using R3.6.1.

RESULTS

Clinicopathologic Data

At 26 institutions, 280 (25 %) distal pancreatectomies were performed for 1114 patients with left-sided primary RPS (Table 2 and Table S1). The median age of the patients was 59 years (range 24–88 years), and 51% of the patients were women. The most frequent histologic subtypes were dedifferentiated liposarcoma (57%), well-differentiated liposarcoma (19%), and leiomyosarcoma (13%). The median tumor size was 25 cm (range 5–68 cm), and the majority of the tumors (68%) were Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade 2 or 3. Neoadjuvant chemotherapy was administered to 42 patients (15%) and radiation to 77 patients (27%).

Complete macroscopic resection (R0/R1) was achieved for 96% of the patients. The median number of organs

TABLE 2 Clinical and pathologic characteristics

Variable	Overall (n = 280) n (%)
Age (years)	
Mean	58.8 ± 12.39
Median (range)	59 (24–88)
Sex	
Female	144 (51.4)
Histology	
Well-differentiated liposarcoma	53 (18.9)
Dedifferentiated liposarcoma	160 (57.1)
Leiomyosarcoma	35 (12.5)
Undifferentiated liposarcoma	11 (3.9)
Other	21 (7.5)
FNCLCC grade	
Unknown	28 (10)
1	62 (22.1)
2	89 (31.7)
3	101 (36.1)
Maximum tumor size (cm)	
Mean	25.1 ± 11.3
Median (range)	24.6 (5.00–68.00)
Margin status	
Unknown	2 (0.7)
R0	90 (32.1)
R1	179 (63.9)
R2	9 (3.2)
Pancreas invaded	
Unknown	12 (4.3)
No	161 (57.5)
Yes	107 (38.2)
Pancreas resected margin status	
Unknown	25 (8.9)
R0	231 (82.5)
R1	24 (8.6)
Administration of radiation	
No	188 (67.1)
Yes	92 (32.9)
Timing of radiation	
Neoadjuvant	77 (83.7)
Adjuvant	9 (9.8)
Palliative	6 (6.5)
90-Day postoperative complication	
Unknown	5 (1.8)
None	100 (35.7)
Clavien-Dindo 1–2	64 (22.9)
Clavien-Dindo ≥3	111 (39.6)
90-Day postoperative pancreatic fistula	
Unknown	6 (2.1)
None/biochemical leak	208 (74.3)
Grade B POPF	52 (18.6)
Grade C POPF	14 (5.0)

FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; POPF, postoperative pancreatic fistula

removed (including the pancreas) was 3 (range, 1–8). The organs most commonly removed were the spleen (96%), the left kidney (88%) and the left colon (81%). The pancreas was invaded in 38% of the patients, and the pancreas margin R0 rate was 83%. The rate of pancreas invasion did not differ between the histologic subtypes (p = 0.66). Concomitant pancreatitis (5%) and incidental tumors (3%) were rare.

Intraoperative Factors and Complication Rates

The distal pancreas was most commonly divided at the body (46%) or tail (34%). Stapling was the most common method of division (85%), with a minority of operations using sealants (9%) and flaps (3%). Somatostatin analogues were used in 45% of the operations, and drains were placed in 96% of surgeries.

For 164 (59%) of the patients, minor or no postoperative complications occurred. The cumulative mortality rates were 1.8% at 30 days, 5.5% at 60 days, and 6.9% at 90 days. The 90-day severe postoperative complication rate (Clavien-Dindo ≥ 3) was 40%. The POPF grade B and C complication rates were respectively 19% and 5%. In the univariable logistic regression models, tumor size, common histologic subtypes, number of organs resected, receipt of preoperative radiation or chemotherapy, use of somatostatin analogues, mode of pancreatic division (staplers, sealants, or tissue flaps), level of pancreatic division (neck, body, or tail), and use of drains did not have an impact on the risk for the development of a complication greater than Clavien-Dindo 3 or a grade B or C POPF (Table 3).

Long-Term Oncologic Outcomes

The median follow-up period was 29.6 months (range, 0.5–126.3 months). The study cohort had a 5-year overall survival of 57%, a freedom from local recurrence of 59%, and a freedom from distant metastasis of 68%. Logistic regression analysis showed no association between clinically relevant POPF and overall survival (Table 4). Multivariable Cox regression models (Table 5) showed that the pancreas R1 margin status was associated with a higher risk of local recurrence (hazard ratio [HR], 2.0; p = 0.042). The 2- and 5-year cumulative incidences of local recurrence for pancreas R0 versus R1 margins were respectively 20% versus 41% and 35% versus 67% (Fig. 1). The only variable significantly associated with risk of distant metastasis was FNCLCC grade 3.

The rates of distal pancreatectomy differed among the 26 institutions. To determine whether this would cause bias, we included the institution that had the largest number of distal pancreatectomies (Fondazione IRCCS Istituto

TABLE 3 Univariable analysis for POPF grades B and C

	OR (95% CI)	*p* value
Age at surgery	0.98 (0.96–1.00)	0.12
Sex (male)	1.04 (0.60–1.81)	0.89
Histology (DDLS)	0.91 (0.43–1.92)	0.80
Histology (LMS)	1.13 (0.42–3.05)	0.82
Histology (UPS)	0.72 (0.14–3.81)	0.70
Histology (other)	2.66 (0.89–7.93)	0.079
Maximum tumor size	1.00 (0.97–1.02)	0.92
Concomitant acute/chronic pancreatitis (yes)	0.25 (0.03–1.96)	0.19
Resected spleen (yes)	2.94 (0.37–23.64)	0.31
Resected left kidney (yes)	0.77 (0.35–1.69)	0.51
Resected left colon (yes)	0.83 (0.42–1.65)	0.60
Resected stomach (yes)	1.13 (0.56–2.29)	0.73
Resected small bowel (yes)	0.60 (0.20–1.83)	0.37
No. of other organs resected	0.88 (0.74–1.06)	0.19
Drain placed (yes)	1.45 (0.30–6.87)	0.64
Division of pancreas reinforced (staple)	0.56 (0.16–1.98)	0.37
Division of pancreas (manual)	0.96 (0.39–2.37)	0.93
Division of pancreas (other)	2.10 (0.57–7.75)	0.26
Level of resection (tail)	0.83 (0.44–1.57)	0.56
Level of resection (uncinate/neck)	0.83 (0.38–1.81)	0.64
Sealant used (yes)	1.98 (0.89–4.41)	0.095
Flap used (yes)	1.92 (0.45–8.28)	0.38
Somatostatin analogue used (yes)	1.26 (0.72–2.21)	0.41
Neoadjuvant chemotherapy (yes)	1.67 (0.82–3.40)	0.16
Neoadjuvant radiation (yes)	0.87 (0.46–1.63)	0.66

OR, odds ratio; CI, confidence interval; DDLS, dedifferentiated liposarcoma; LMS, leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma

Nazionale dei Tumori) in the univariable analysis, and it did not change the results (HR, 0.65; $p = 0.17$).

DISCUSSION

The reported data represent the cumulative 10-year experience of 26 sarcoma centers located across three continents. Between 2008 and 2017, 280 patients underwent distal pancreatectomy for primary RPS. The denominator for this study cohort was 1114 left-sided RPS cases, suggesting that distal pancreatectomy is common (25%) in the treatment of a left-sided RPS.

Unlike RPS, for which no dedicated studies exist due to its rarity, resection of the distal pancreas for the treatment of more common primary pancreatic diseases has been very well described. Studies of primary pancreatic disease spanning two decades, show morbidity rates of 31–53%, POPF rates of 5–24%, and mortality rates of 0.9–3.5%.[1–4] A single-institution, prospective study of 43 patients with non-pancreas primary retroperitoneal tumors who underwent distal pancreatectomy (17 of which were RPS) reported 30-day morbidity for 9 patients (21%), POPF B or C for 14 patients (33%), and 30-day death for 1 patient (2%).[13] Complications were collected prospectively. However, the sample was small, limiting the power to detect statistical differences.

In contrast, our multi-institutional study, although retrospective, was large. We observed severe morbidity in 111 patients (40%), clinically relevant POPF in 66 patients (24%), and 30-day death in 5 patients (1.8%). Using the primary pancreatic disease studies as a benchmark, the results taken together appear to show that distal pancreatectomy for primary RPS has a similar safety profile. In other words, severe morbidity and POPF are common, and mortality is low.

In our study, the clinicopathologic characteristics (receipt of neoadjuvant therapy, level of transection, common histologic subtypes) and the factors that mitigate POPF (use of drains, somatostatin analogues, and flaps) were not associated with the development of POPF. These results are similar to those reported by other studies that investigated POPF after distal pancreatectomy. In an analysis of 2026 distal pancreatectomies for a variety of conditions, multivariable analyses did not identify risk factors

TABLE 4 Univariable analysis for long-term outcomes

	Local recurrence		Distant metastasis		Overall survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at surgery	1.00 (0.99–1.02)	0.79	1.01 (0.99–1.03)	0.18	1.03 (1.01–1.05)	0.004
Sex (male)	0.97 (0.63–1.49)	0.88	1.20 (0.73–1.97)	0.47	0.99 (0.64–1.51)	0.95
Histology (DDLS)	1.98 (1.06–3.69)	0.033	6.47 (1.55–27.12)	0.011	3.16 (1.43–6.97)	0.004
Histology (LMS)	0.74 (0.26–2.10)	0.57	24.79 (5.75–106.79)	< 0.001	4.78 (1.96–11.65)	< 0.001
Histology (UPS)	3.05 (1.14–8.13)	0.026	9.62 (1.61–57.62)	0.013	3.52 (1.03–12.04)	0.045
Histology (other)	0.96 (0.31–2.98)	0.94	18.00 (3.88–83.48)	< 0.001	3.67 (1.33–10.14)	0.012
FNCLCC (grade 2)	1.27 (0.67–2.40)	0.47	4.77 (1.41–16.21)	0.012	1.56 (0.73–3.32)	0.25
FNCLCC (grade 3)	1.84 (0.99–3.40)	0.052	12.27 (3.77–39.96)	< 0.001	4.83 (2.42–9.61)	< 0.001
Maximum tumor size	1.04 (1.02–1.06)	< 0.001	0.95 (0.93–0.98)	< 0.001	1.00 (0.98–1.02)	0.86
Margin assessment (R2)	3.06 (1.23–7.59)	0.016	1.56 (0.49–4.99)	0.45	1.86 (0.75–4.59)	0.18
Pancreas invaded (yes)	1.42 (0.90–2.24)	0.13	1.13 (0.67–1.91)	0.64	1.94 (1.24–3.02)	0.003
Pancreas margin (R1)	2.37 (1.24–4.52)	0.009	0.95 (0.38–2.39)	0.92	1.28 (0.61–2.66)	0.51
Any chemotherapy (yes)	1.90 (1.23–2.95)	0.004	1.98 (1.20–3.26)	0.008	1.41 (0.91–2.18)	0.12
Any radiation (yes)	0.82 (0.51–1.30)	0.39	1.16 (0.70–1.93)	0.56	0.66 (0.41–1.06)	0.083
90-day postop complication (CD 1–2)	1.17 (0.65–2.08)	0.60	1.13 (0.57–2.24)	0.72	1.00 (0.55–1.81)	> 0.99
90-day postop complication (CD ≥ 3)	1.47 (0.88–2.44)	0.14	1.63 (0.92–2.88)	0.095	1.58 (0.96–2.59)	0.070
POPF (grades B and C)	1.57 (0.95–2.59)	0.076	1.70 (0.99–2.92)	0.054	1.55 (0.96–2.51)	0.074

HR, hazard ratio; CI, confidence interval; DDLS, LMS, UPS, FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; CD, Clavien-Dindo; POPF, postoperative pancreatic fistula

TABLE 5 Multivariable analysis for long-term outcomes

	Local recurrence		Distant metastasis		Overall survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at surgery	–		–		1.02 (1.00–1.04)	0.023
Sex (male)	–		–			
Histology (DDLS)	1.85 (0.94–3.64)	0.073	1.22 (0.11–13.73)	0.87	1.80 (0.46–7.03)	0.40
Histology (LMS)	1.04 (0.27–4.01)	0.96	2.80 (0.23–33.84)	0.42	2.08 (0.47–9.26)	0.34
Histology (UPS)	5.38 (1.85–15.68)	0.002	0.77 (0.05–12.92)	0.85	1.23 (0.20–7.54)	0.82
Histology (other)	2.17 (0.65–7.28)	0.21	2.38 (0.20–28.77)	0.50	1.83 (0.40–8.30)	0.43
FNCLCC (grade 2)	–		3.73 (0.49–28.45)	0.20	1.01 (0.30–3.45)	0.98
FNCLCC (grade 3)	–		7.53 (1.01–56.17)	0.049	2.73 (0.83–8.99)	0.098
Maximum tumor size	1.05 (1.03–1.07)	< 0.001	0.98 (0.95–1.01)	0.11	–	
Margin assessment (R2)	3.86 (1.14–13.06)	0.030	–		–	
Pancreas invaded (yes)	–		–		1.54 (0.96–2.46)	0.074
Pancreas margin (R1)	2.02 (1.03–3.97)	0.042	–		–	
Any chemotherapy (yes)	1.53 (0.92–2.53)	0.10	0.99 (0.56–1.76)	0.98	–	
Any radiation (yes)	–		–		–	
90-day postop complication (CD 1–2)	–		–		–	
90-day postop complication (CD ≥ 3)	–		–		–	
POPF (grades B and C)	–		1.45 (0.78–2.69)	0.24	–	

HR, hazard ratio; CI, confidence interval; DDLS, LMS, UPS, FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; CD, Clavien-Dindo; POPF, postoperative pancreatic fistula

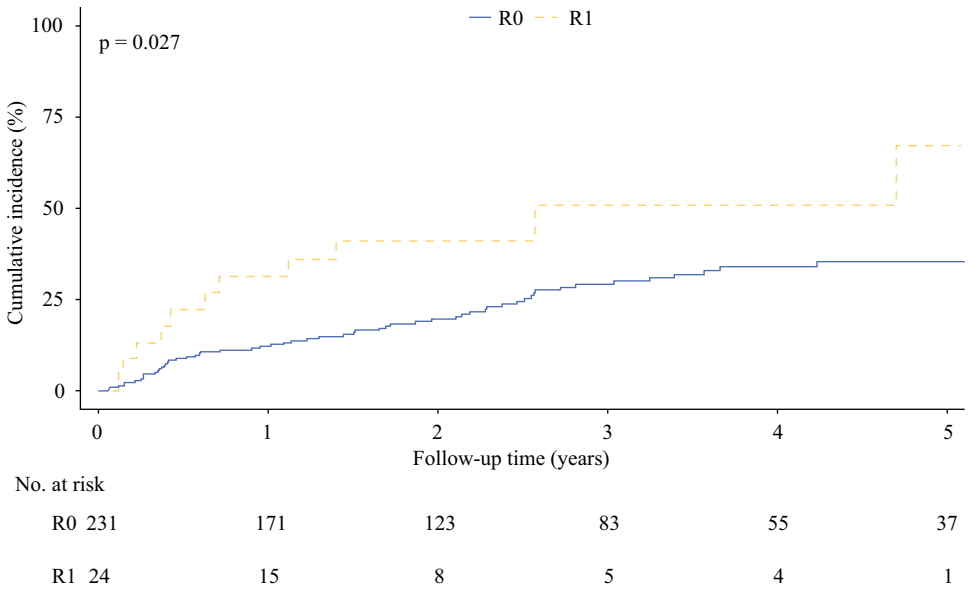

FIG. 1 Local recurrence by resected pancreas margin

associated with POPF.[4] The International Study Group of Pancreatic Surgery consensus guidelines highlight the lack of clear evidence linking a risk factor or mitigating factor with POPF.[14] These data and our data suggest that the development of POPF may be stochastic, and that techniques yet to be determined are needed to prevent POPF.

The reported rate of any organ invasion for RPS is approximately 50%.[15,16] When invasion of the pancreas is specifically analyzed, Fairweather et al.[15] reported a 30% invasion rate (3/10), the French Sarcoma Group[16] reported a 15% invasion rate (5/33), and Berselli et al.[17] reported a 46% invasion rate (26/56). We report a similar rate of invasion (38%). It must be noted that cases included the Fairweather cohort. Interestingly, we also were able to report on the status of the resected pancreas margin, with our findings showing that the pancreas R0 and R1 margin rates were respectively 83% and 9% (9% were unknown). Although this study could not truly ascertain the rate of pancreas invasion for all left-sided primary RPS, it appears that the patients managed with a distal pancreatectomy had a high rate of pancreas invasion and that a negative microscopic margin at the level of the pancreas could be achieved in the vast majority of cases.

Similar to other reports, the presence of organ invasion did not have an impact on local recurrence in our study.[15] In the univariable analysis, the presence of pancreas invasion was not associated with local recurrence (p = 0.13). However, when we analyzed the margin of the resected pancreas, we found that 9% of the patients (n = 24) had a positive microscopic margin and that an R1 pancreas margin was associated with a doubled risk of local recurrence (HR, 2.0; p = 0.042). The increase in local recurrence may have been a reflection of a more invasive biology or technical failure. These data do not allow us to comment on the relationship between the pancreas margin and local recurrence. Also, these results need to be viewed with the understanding that the pathology slides did not undergo centralized review, so the criteria to determine invasion could have been subjective.

A TARPSWG study of 1007 consecutive resections for primary RPS (2002–2011) reported no impact of postoperative adverse events on overall survival, local recurrence, or distant metastases.[7] Our results were similar. When we studied the impact of POPF on long-term oncologic outcomes, we found that clinically relevant POPF was not associated with overall survival, local recurrence, or distant metastasis. Thus, although POPF can lead to a prolonged recovery and a poor quality of life, it does not appear to have an impact on long-term oncologic outcomes. It should be noted that in the univariable analysis, POPF and overall survival had a hazard ratio of 1.55 (p = 0.074). Although this is not significant, perhaps further studies may identify a significant association.

The major limitation of this study was its retrospective nature. It did not report on intraoperative details such pancreas texture or whether the pancreatic duct was ligated. It also did not report on postoperative details such as hospital length of stay, readmission, interventional procedures, rehabilitation, or quality of life. Finally, it did not report on the location of the local recurrence, specifically whether the local recurrence was in the pancreatic bed.

However, the study represents a large, international sarcoma experience that improves our understanding of a rare disease. The study identified three major findings. First, it showed that the rate of major complications and clinically relevant POPF after distal pancreatectomy for

primary RPS compares favorably with studies evaluating distal pancreatectomy for primary pancreatic disease and that these postoperative complications do not have an impact on overall survival. Second, it showed that factors to mitigate POPF were not successful and that further research is needed to develop better techniques to avoid this complication. Third, it showed that the pancreas is commonly invaded by RPS.

In conclusion, distal pancreatectomy in the setting of complex multi-visceral resection is a reasonable approach to facilitate the complete removal of primary RPS.

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REFERENCES

1. Kleeff J, et al. Distal pancreatectomy: risk factors for surgical failure in 302 consecutive cases. *Ann Surg*. 2007;245:573–82.
2. Lillemoe KD, et al. Distal pancreatectomy: indications and outcomes in 235 patients. *Ann Surg*. 1999;229:693–8; discussion 698–700.
3. Reeh M, et al. High surgical morbidity following distal pancreatectomy: still an unsolved problem. *World J Surg*. 2011;35:1110–7.
4. Ecker BL, et al. Risk factors and mitigation strategies for pancreatic fistula after distal pancreatectomy: analysis of 2026 resections from the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg*. 2019;269:143–9.
5. Gronchi A, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the Multi-Institutional Collaborative RPS Working Group. *Ann Surg*. 2016;263:1002–9.
6. Tseng WW, Pollock RE, Gronchi A. The Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG): "red wine or white"? *Ann Surg Oncol*. 2016;23:4418–20.
7. MacNeill AJ, et al. Postoperative morbidity after radical resection of primary retroperitoneal sarcoma: a report from the Transatlantic RPS Working Group. *Ann Surg*. 2018;267:959–64.
8. Trans-Atlantic Retroperitoneal Sarcoma Working Group. Management of metastatic retroperitoneal sarcoma: a consensus approach from the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). *Ann Oncol*. 2018;29:857–71.
9. van Houdt WJ, et al. New research strategies in retroperitoneal sarcoma: the case of TARPSWG, STRASS, and RESAR: making progress through collaboration. *Curr Opin Oncol*. 2019;31:310–6.
10. Raut CP, et al. Predicting survival in patients undergoing resection for locally recurrent retroperitoneal sarcoma: a study and novel nomogram from TARPSWG. *Clin Cancer Res*. 2019;25:2664–71.
11. Haas RLM, et al. Radiotherapy for retroperitoneal liposarcoma: a report from the Transatlantic Retroperitoneal Sarcoma Working Group. *Cancer*. 2019;125:1290–300.
12. Bassi C, et al. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery*. 2017;161:584–91.
13. Keung EZ, et al. Postoperative pancreatic fistula after distal pancreatectomy for non-pancreas retroperitoneal tumor resection. *Am J Surg*. 2020;220:140–6.
14. Miao Y, et al. Management of the pancreatic transection plane after left (distal) pancreatectomy: expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2020.
15. Fairweather M, et al. Incidence and adverse prognostic implications of histopathologic organ invasion in primary retroperitoneal sarcoma. *J Am Coll Surg*. 2017;224:876–83.
16. Toulmonde M, et al. Retroperitoneal sarcomas: patterns of care at diagnosis, prognostic factors, and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. *Ann Oncol*. 2014;25:735–42.
17. Berselli M, et al. Morbidity of left pancreatectomy when associated with multivisceral resection for abdominal mesenchymal neoplasms. *JOP*. 2011;12:138–44.