

Is Routine Splenectomy Justified for All Left-Sided Pancreatic Cancers? Histological Reappraisal of Splenic Hilum Lymphadenectomy

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ABSTRACT

Background. Although splenectomy is recommended during resection for left-sided resectable pancreatic ductal adenocarcinoma (PDAC) to perform lymphadenectomy of station 10 (splenic hilum), no level I evidence justifies this procedure. This study aims to evaluate the rate of lymph node (LN) and contiguous involvement of the splenic hilum in resectable distal PDAC.

Methods. We retrospectively reviewed all patients who underwent splenopancreatotomy for PDAC in the past 10 years. Station 10 LN were routinely isolated, and all corresponding microscopic slides were reinterpreted by a pathologist. The computed tomography (CT) results of patients with tumoral involvement of the spleen or splenic hilum by contiguity (TISOSH) and ≤ 10 mm between the

tumor and spleen on pathology were blindly reviewed by two radiologists to evaluate CT for diagnosis of TISOSH.

Results. We included 110 consecutive patients, including 104 with analyzable station 10 LN. The tumor was N+ in 58 (53%) patients. The median number of LN identified at station 10 was 2.0 ± 3.0 . No station 10 LNs were detected in 42 (40%) patients. No patients had tumor-positive LN at station 10. TISOSH was found in nine (8%) patients, and was significantly associated with tail location ($p = 0.001$), tumor size ($p = 0.005$), and multivisceral involvement ($p = 0.015$). For diagnosis of TISOSH, the sensitivity and specificity of CT were respectively 89% and 95% for radiologist 1 and 89% and 100% for radiologist 2.

Conclusions. Splenic preservation during resection of distal PDAC may be an option in selected patients with body tumors and no suspected splenic or splenic hilum involvement on preoperative CT.

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Until now, splenectomy has been indicated for malignant lesions to ensure R0 resection of the primary tumor and lymphadenectomy. Nevertheless, there is no strong evidence to support this indication. First, for lymphadenectomy, the risk of splenic hilum LN involvement has been poorly evaluated, with incidence ranging from 0 to 10% in certain very small series,^{1,2} series including stage IV tumors,³ or in collective series without standardized pathologic examination.² Second, although possible tumoral involvement of the spleen or contiguous involvement of the splenic hilum (TISOSH) can justify

splenectomy, this could be predicted by combined preoperative imaging and intraoperative assessment. However, we did not find any studies evaluating this question.

Nevertheless, splenectomy is not harmless. Preservation of the spleen is associated with less intraoperative bleeding, lower morbidity, shorter hospital stay,^{4,5} as well as reduced risk of thromboembolic complications⁶ and overwhelming post splenectomy infection, which is a rare but potentially lethal complication.⁷ Until now, preservation of the spleen (with or without splenic vessel preservation) is only recommended in case of benign or premalignant lesions.⁵

The main goal of this study is to evaluate the rates of LN involvement and contiguous involvement of the splenic hilum in resectable distal PDAC. The second aim is to evaluate the accuracy of preoperative imaging for prediction of TISOSH.

PATIENTS AND METHODS

Study Population

After institutional review board approval (IRB 12-055), all patients who underwent splenopancreatectomy for nonmetastatic ductal adenocarcinoma of the neck, body or tail of the pancreas from January 2008 to March 2017 at Beaujon Hospital, Clichy, France were included in the study. All surgical indications were decided by a multidisciplinary tumor board. Neoadjuvant or induction treatment by chemo- and/or radiotherapy were not exclusion criteria.

Data including demographics, comorbidities, preoperative imaging, operative characteristics, and histology were retrospectively collected from medical charts and analyzed.

Splenopancreatectomy was always performed by a standardized technique. Lymphadenectomy always included at least the following stations (according to the Japanese Pancreas Society nomenclature of peripancreatic LN,⁸ presented in Fig. 1): splenic hilum (station 10), along the splenic artery (station 11), and along the inferior border of the body and tail (station 18). LN around celiac trunk (station 9) were harvested if the tumor was located in the body.

Pathological Analysis

All distal pancreatectomies with attached spleen specimens were received and analyzed in fresh and unfixed state. Each organ was measured individually. The exact location, appearance and size of the tumor, its distance from the pancreatic transection margin, and any invasion of the peripancreatic tissue were specified, including presence (or absence) of invasion of the splenic hilum and/or

parenchyma. Posterior and anterior resection margins were systematically painted with ink. The entire specimen was fixed for 48 h in 4% formalin solution, then the specimen was transversely cut in consecutive 5-mm-thick slices starting from the proximal resection margin up to the distal pancreas. Pancreatic transection margins and tumors in relation to the anterior and posterior margins and the spleen were systematically sampled. All peripancreatic adipose tissue was sampled to identify any peripancreatic LN (stations 11 and 18). All adipose tissue and LN from the splenic hilum (station 10) were sampled separately from the peripancreatic lymph nodes and routinely identified as “splenic hilum.” All tissue samples were embedded in paraffin then sectioned and stained with hematein and eosin.

Microscopic examination of cancer specimens and reports were performed according to the standardized protocol of the College of American Pathologists based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor–node–metastasis (TNM) 7th edition.⁹ Resection was considered to be R0 when the distance of the tumor from the surgical margin was ≥ 1 mm.

To allow precise evaluation of station 10 LN involvement, all slides identified as “splenic hilum” were prospectively reanalyzed by an experienced pathologist (N.G.) to count the number of LN in the station, determine whether they were metastatic, and assess presence of TISOSH.

Imaging

All patients underwent at least one contrast-enhanced computed tomography (CT) scan of the chest and abdominopelvic cavity within 1 month before surgery, which was available in the digital imaging storage system of our institution. Magnetic resonance imaging (MRI) and endoscopic ultrasound were performed selectively. Data were retrospectively collected from imaging reports written by the radiologist who had performed the examination.

Moreover, two radiologists independently reevaluated preoperative CT results for diagnosis of TISOSH. For this, all CTs of patients with TISOSH confirmed by pathological examination were isolated, as well as those of patients with distance from the left side of the tumor to the spleen ≤ 10 mm on pathological analysis but without TISOSH. CTs of patients with tumor > 10 mm from the spleen hilum were excluded from the analysis because absence of splenic invasion was easy to confirm. CTs were anonymized and reviewed in random order, and the radiologists were asked to say whether the spleen or splenic hilum was invaded by the tumor (Fig. 2a) or not (Fig. 2b). The radiologists were blinded to pathological data.

FIG. 1 Nomenclature of peripancreatic lymph nodes according to the Japan Pancreas Society.⁸ Lymph node (LN) stations: no. 5: suprapyloric LN, no. 6: infrapyloric LN, no. 7: LN along the left gastric artery, no. 8: LN along the common hepatic artery, no. 9: LN around the celiac artery, no. 10: LN at the splenic hilum, no. 11: LN along the splenic artery, no. 12: hepatoduodenal ligament LN, no. 13: LN on the posterior aspect of the head of the pancreas, no. 14: LN along the superior mesenteric artery, no. 15: LN along the middle colic artery, no. 16: aortocaval LN, no. 17: LN on the anterior aspect of the head of the pancreas, no. 18: LN along the inferior edge of the pancreas

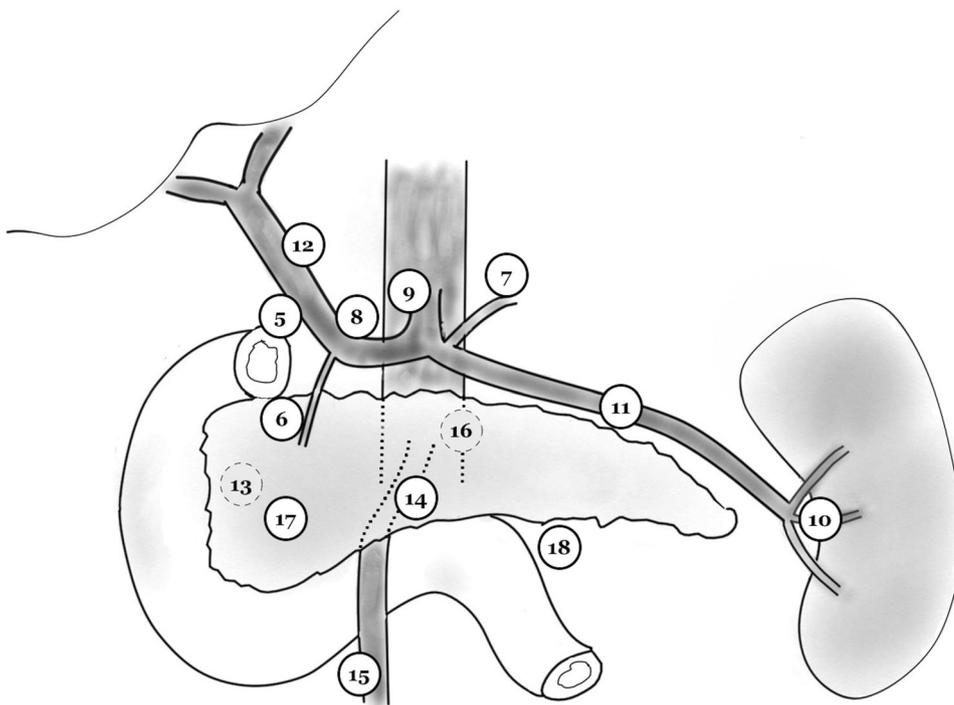
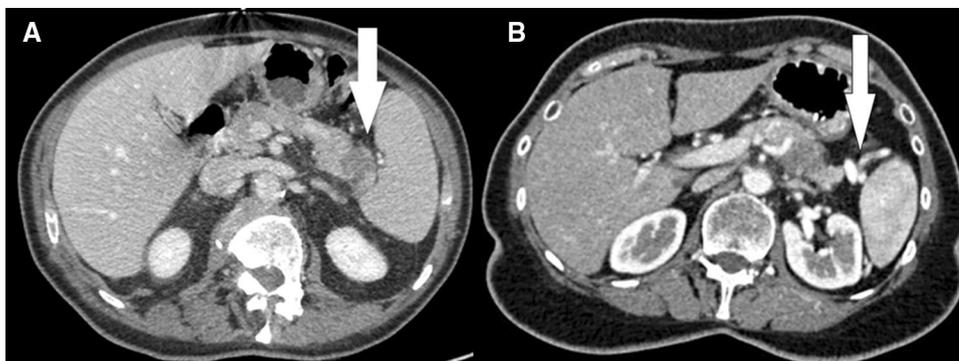


FIG. 2 Abdominal CT scan of patients operated for a pancreatic adenocarcinoma with **a** and without **b** involvement of the splenic hilum by contiguity proven by pathological analysis of operative specimens



Statistical Analysis

Quantitative data are expressed as mean \pm standard deviation (SD) and were compared using the Mann-Whitney *U* test. Qualitative data are reported as frequencies and percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. All tests were two sided. *p* Value $<$ 0.05 was considered to be statistically significant.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using 2×2 contingency tables. Interradiologist agreement was analyzed using weighted kappa statistics with coefficient of 0.00–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00 indicating slight, fair, moderate, substantial, and almost perfect agreement.

All analyses were performed using SPSS (version 23, IBM Corp, Armonk, NY, USA).

RESULTS

Demographic, Preoperative and Surgical Characteristics

A total of 110 consecutive patients underwent splenopancreatectomy for distal PDAC. The mean age of patients was 65 ± 10 years, and 59 (54%) were men. Other clinical characteristics are summarized in Table 1.

Pancreatic MRI and endoscopic ultrasound was performed in 78 (71%) and 61 patients (55%), respectively. Fifty (82%) of these 61 patients had a biopsy of the lesion, and 47 were diagnosed with PDAC. Overall, 57% of the

patients underwent surgery without preoperative histological confirmation.

The pancreatic lesion was located in the neck, body, and tail on CT in 9 (8%), 55 (50%), and 46 (42%) patients, respectively. LN involvement was suspected on the CT report in only seven cases (6%). The suspected LN metastases were located at station 18 (inferior body LN) in five patients, and station 9 (celiac trunk LN) in two patients. No suspected LN metastases were described in station 10 (splenic hilum) on preoperative CT.

Surgical characteristics are described in Table 1.

TABLE 1 Demographic and surgical characteristics of 110 patients who underwent distal splenopancreatectomy for ductal adenocarcinoma

	<i>n</i> = 110
Gender	
Male	59 (54) ^a
Female	51 (46)
Age (years)	65 ± 10 (37–88) ^b
Body mass index (kg/m ²)	25 ± 5 (17–39)
ASA score	
1–2	94 (85)
3–4	16 (15)
Comorbidity	46 (42)
Cardiovascular	25 (23)
Diabetes	25 (23)
Asthma/COPD	6 (5)
Neurological	4 (4)
Smoking	38 (35)
Neoadjuvant/induction treatment	28 (25)
Radiochemotherapy	17 (15)
Chemotherapy	11 (10)
Surgical approach	
Laparotomy	87 (79)
Laparoscopy	23 (21)
Multivisceral resection	26 (24)
Left adrenal gland	15 (14)
Left colonic flexure	8 (7)
Stomach	8 (7)
Duodenojejunal junction	5 (5)
Left kidney	2 (2)
Vascular resection	14 (13)
Mesenteric–portal confluence	12 (11)
Celiac trunk	3 (3)

^aNumber of cases (percentage of cases)

^bMean ± standard deviation (range)

ASA American Society of Anesthesiologists, COPD chronic obstructive pulmonary disease

Pathological Examination

The mean length of the resected pancreas was 113 ± 28 mm (range 70–180 mm). Associated intraductal papillary mucinous neoplasms were observed in 12 patients (11%). The characteristics of PDAC are listed in Table 2.

The mean number of LN harvested was 23 ± 13 (range 3–80). LN metastases were identified in 58 patients (53%) by pathological examination. The mean number of metastatic LN in patients with LN involvement was 3.4 ± 2.7 (range 0–12). LN metastases were found in the peripancreatic area, including station 11 (along the splenic artery)

TABLE 2 Pathological characteristics of the 110 resected specimens

	<i>n</i> = 110
Tumor size (mm)	34 ± 16 (7–75) ^a
Differentiation (<i>n</i> = 101)	
Moderately/poorly differentiated	53 (52) ^b
Well differentiated	48 (48)
Vascular invasion	72 (65)
Perineural invasion	90 (82)
Multivisceral invasion	23 (21)
Spleen or splenic hilum	9 (8)
Left adrenal gland	6 (5)
Duodenojejunal junction	5 (5)
Stomach	4 (4)
Left colonic flexure	3 (3)
Splenic vein invasion	14 (13)
Splenic artery invasion	7 (6)
T stage ^c	
1	4 (4)
2	6 (5)
3	94 (85)
4	6 (5)
Total lymph nodes analyzed	23 ± 13 (3–80)
N stage ^c	
0	52 (47)
1	58 (53)
Number of metastatic LN	
1–3	36 (62)
4–6	13 (22)
≥ 7	9 (16)
Status of margin resection	
No tumor (R0)	73 (66)
Microscopic involvement (R1)	37 (34)
Macroscopic involvement (R2)	0 (0)

^aMean ± standard deviation (range)

^bNumber of cases (percentage of cases)

^cAJCC cancer staging (7th edition)

and station 18 (inferior pancreatic body) in 57 patients and in station 9 (celiac trunk) in 5 patients. The initial pathological report concluded that no station 10 LNs were present in 38 patients, whereas 59 had at least one station 10 LN (nonmetastatic in all), and did not give specific results regarding station 10 LN in 13 patients. Reexamination of the resected specimens resulted in correct analysis of metastases in station 10 (splenic hilum) in 104 patients (95%). Six other patients were excluded from this analysis because correct reexamination of station 10 was not possible due to a problem of identification ($n = 4$) or of archiving ($n = 2$) of the splenic hilum slices. Among these six patients, two were classified as N– and four only had metastatic nodes in the peripancreatic area according to pathological reports.

The mean and median number of nodes identified at station 10 were 2.5 ± 3.0 (0–12) and 2.0, respectively. No nodes were detected at station 10 by reviewing of slices in 42 patients (40%). TISOSH was identified in nine patients (8%). No metastatic LNs were found in station 10 in either the TISOSH group or the no-TISOSH group.

Evaluation of TISOSH

Comparison of clinical, biological, imaging, and pathological criteria between the patients with and without TISOSH is presented in Table 3.

There were no differences in clinical or biological characteristics between groups. The total number of LN analyzed from the operative specimen did not differ between the TISOSH and no-TISOSH group: 22 ± 16 (range 10–51) versus 24 ± 13 (3–80), respectively ($p = 0.673$). Tail localization was significantly associated with TISOSH ($p = 0.001$). Lesion size on preoperative CT was on average 17 mm larger in the TISOSH group than in the no-TISOSH group ($p = 0.005$). Multivisceral resection, including resection of the stomach, left colonic flexure, left kidney, left adrenal gland, or duodenojejunal junction, was significantly associated with TISOSH ($p = 0.001$).

Involvement of an adjacent organ (including the stomach, left colonic flexure, left kidney, left adrenal gland, or duodenojejunal junction) was the only pathological criterion significantly associated with TISOSH ($p = 0.015$).

Two radiologists blindly reviewed 29 preoperative CT, including those from the 9 patients of the TISOSH group and 20 retrieved from patients in the no-TISOSH group but with distance from the left side of the tumor to the spleen ≤ 10 mm. Radiologist 1 and radiologist 2 respectively identified 8/9 patients and 8/9 patients in the TISOSH group and 19/20 patients and 20/20 patients in the no-TISOSH group. The resulting sensitivity was 89% for radiologists 1 and 2; the specificity was 95% for radiologist 1 and 100% for radiologist 2. The positive predictive value

was 89% for radiologist 1 and 100% for radiologist 2; the negative predictive value was 95% for radiologists 1 and 2. Interradiologist agreement for radiological diagnosis of TISOSH was almost perfect ($\kappa = 0.917$).

DISCUSSION

In the present series including 110 consecutive patients who underwent splenopancreatectomy for left-sided PDAC at a single high-volume center, LN located in station 10 (splenic hilum) were always metastasis free. Furthermore, TISOSH was observed in only 8% of cases and only in patients with a tumor in the tail. Moreover, its presence could be accurately predicted by CT and intraoperative findings. Our results, which represent the largest study specifically evaluating station 10 LN involvement and TISOSH, do not support routine splenectomy during left-sided pancreatic resection in patients with PDAC.

Data on invasion of station 10 LN from distal PDAC are scarce but strongly suggest that this invasion is exceptional. Onesti et al. analyzed 10 specimens of splenopancreatectomy for PDAC and only identified one station 10 LN metastasis.¹ Fujita et al. retrospectively studied the pathological reports of 50 patients who underwent splenopancreatectomy for PDAC and did not observe any station 10 LN metastases.¹⁰ Similarly, Kim et al. performed 12 splenopancreatectomies for PDAC and did not identify any station 10 LN metastases.² The same publication also reported a collective series from three Japanese centers including 85 patients with only four (5%) station 10 LN metastases (including 3 with TISOSH). However, in that collective study, the pathological examination protocol was not standardized. The largest study on this topic included 85 patients who underwent resection for distal as well as central PDAC, including 19% with stage IV disease and 11% who underwent total pancreatectomy. Despite routine LN dissection, station 10 LN were identified in 62 (73%) patients, including only 2 (3%) with metastases.³

The present study confirms that station 10 LNs are not present in all patients. Indeed, we did not find any station 10 LN in 42 (40%) out of 104 patients despite a standardized pathological examination.⁹ In the study of Sahin et al., 85 patients had distal pancreatectomy (DP) with meticulous LN dissection but 23 (27%) had no analyzable station 10 LNs.³ The higher rate (40%) we observed in the present study could be a consequence of the neoadjuvant treatment performed in 25% of the patients.¹¹ Thus, even though both the number of retrieved LN and the LN ratio have been shown to be important prognostic factors, routine resection of the splenic hilum does not increase the total number of retrieved LN in many patients, and therefore does not improve LN staging.^{12–14} Also, the mean

TABLE 3 Risk factors of tumoral involvement of the spleen or splenic hilum (TISOSH) by contiguity

	No-TISOSH ^a group <i>n</i> = 101	TISOSH group <i>n</i> = 9	<i>p</i> -Value
Clinical presentation			
Age (years)	65 ± 10 (37–88) ^b	62 ± 10 (51–76)	0.351
Sex (male/female)	53 (52) ^c /48 (48)	6 (67)/3 (33)	0.500
Body mass index (kg/m ²)	25 ± 5 (17–39)	25 ± 4 (18–31)	0.557
Smoking	32 (32)	6 (67)	0.062
Neoadjuvant treatment	24 (24)	4 (44)	0.226
Biology			
CA 19-9 (IU/mL)	247 ± 54 (1–5000)	399 ± 120 (4–1600)	0.954
CT scan			
Tumor size (mm)	30 ± 12 (10–60)	47 ± 16 (22–77)	0.005
Tumor localization			0.001
Neck/body	64 (63)	0 (0)	
Tail	37 (37)	9 (100)	
Surgery			
Multivisceral resection ^d	19 (19)	7 (77)	0.001
Pathology			
Tumor size (mm)	33 ± 15 (7–75)	44 ± 18 (25–75)	0.070
Multivisceral invasion ^d	10 (10)	4 (44)	0.015
T stage ^e			1.000
T1/T2	10 (9)	0 (0)	
T3/T4	91 (91)	9 (100)	
Vascular invasion	64 (63)	8 (89)	0.159
Perineural invasion	83 (82)	7 (78)	0.666
R1 (1 mm resection margin)	34 (34)	3 (33)	1.000
Differentiation (<i>n</i> = 101)			
Moderately/poorly differentiated	49 (48)	4 (44)	
Well differentiated	43 (43)	5 (56)	
Lymph node metastasis (N+)	53 (52)	5 (56)	1.000
Total lymph nodes analyzed	24 ± 13 (3–80)	22 ± 16 (10–51)	0.673
Number of metastatic lymph nodes	1.8 ± 2.6 (0–12)	2.1 ± 2.7 (0–8)	0.690
Lymph node ratio	0.08 ± 0.12 (0–0.64)	0.09 ± 0.11 (0–0.33)	0.850

^aTISOSH, tumoral involvement of the spleen or of the splenic hilum by contiguity

^bMean ± standard deviation (range)

^cNumber of cases (percentage of cases)

^dIncluding stomach, left colonic flexure, left kidney, left adrenal gland, and duodenojejunal junction

^eAJCC cancer staging (7th edition)

number of station 10 LN harvested in our study was 2.5 (including the 40% of patients without station 10 LN), which is consistent with the data of other series (mean of 2.2 and 3.3 for station 10 LN for Fujita et al.¹⁰ and Kim et al.,² respectively). Thus, it seems unlikely that our evaluation of the splenic hilum LN number was underestimated. Finally, none of the 62 patients with at least one analyzable station 10 LN had LN metastases, even those with TISOSH. The lack of stage migration and of improved prognosis following “complete” station 10 LN harvesting is supported by a recent randomized controlled study

evaluating routine splenectomy in the treatment of proximal gastric adenocarcinoma.¹⁵ In that trial, the median number of station 10 LN harvested was two after LN dissection with splenic preservation versus four in the splenectomy arm, with no difference in the pN0/N1/N2–3 distribution or long-term survival.

Another justification for performing routine splenectomy during pancreatectomy for distal PDAC is obtaining negative surgical margins in patients with TISOSH. However, TISOSH was only observed in 8% of patients in the current series, and its presence could be reliably predicted

by CT with excellent positive and negative predictive values, and almost perfect interradiologist agreement ($\kappa = 0.917$). TISOSH was never observed in tumors of the pancreatic body, thus the association of CT and intraoperative findings seems to be accurate enough to avoid R1 resection at this level.

Various studies have already emphasized the importance of preserving the spleen whenever possible, because of its hematological and immunological roles.¹⁶ Postsplenectomy sepsis due to encapsulated bacteria is a rare but severe complication that occurs within the first 2 years after splenectomy in most cases, even after adequate vaccination.¹⁷ Splenectomy also leads to perioperative hematological abnormalities that can persist for years, such as high platelet count resulting in a hypercoagulability state with risk of thromboembolic complications.^{18–21} More importantly, splenectomy has already been associated with diminished or at least no improvement in survival after curative resection for gastric cancer.^{15,22} In the field of PDAC, splenectomy has been identified as an independent factor predictive of decreased long-term survival.²³

Spleen preservation is highly feasible through both the open and laparoscopic approaches with a feasibility rate ranging from 78% to 100%.^{24–26} Two techniques have been described for spleen preservation. The technique by Warshaw et al.²⁵ requires splenic vessel ligation and resection, while the second technique by Kimura et al.²⁷ does not, as it involves preservation of the splenic vessels by careful dissection along them. The Warshaw technique allows spleen preservation in up to 98% of cases.²⁵ Although the Warshaw technique is associated with slightly higher morbidity than the Kimura technique because of a higher rate of splenic infarction,^{26–28} the splenic vessels cannot be preserved during pancreatectomy for left-sided PDAC. This choice is strongly justified by two reasons. First, it is important to provide a correct posterior margin and to reduce the risk of posterior R1 or R2 resection. Second, complete lymphadenectomy along the splenic vessels (station 11) must be performed. Hence, the Warshaw technique is a potential alternative to splenopancreatectomy for selected PDAC. The Warshaw technique seems to be particularly useful in patients with body tumors, because early neck transection followed by immediate ligation and sectioning of the splenic vessels limits intraoperative bleeding,²⁹ especially during dissection of the distal branches in the splenic hilum.

The present study has certain limitations. First, it has a retrospective design and the patients were included during a 10-year period; however, slides were reanalyzed by a pathologist specialized in digestive pathology to limit the risk of misdiagnosis. Also, this study includes 25% of patients who received neoadjuvant treatment, which could modify histological findings compared with treatment-

naïve patients.³⁰ This could explain in part the 40% rate of patients with no station 10 LN on pathological examination. However, the role of neoadjuvant therapy in PDAC is progressively increasing, including in stage I and II disease,³⁰ so our conclusions are probably applicable to the clinical reality. Lastly, this study was not designed to highlight a potential reduction of circumferential margins due to spleen preservation.

In conclusion, the results of this study suggest that routine splenectomy is not mandatory during distal pancreatectomy for PDAC, since fewer patients have splenic hilum station 10 LNs than previously expected. Also, these nodes do not seem to be an important drainage basin for body/tail PDAC, and preoperative CT is accurate to diagnose TISOSH. The Warshaw technique could be an alternative to conventional splenopancreatectomy in selected cases, particularly in tumors limited to the pancreatic body. However, a randomized controlled trial is requisite to validate the oncological safety of spleen-preserving surgery in distal PDAC.

DISCLOSURE None reported.

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