

Outcomes after distal pancreatectomy with or without splenectomy for intraductal papillary mucinous neoplasm: international multicentre cohort study

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Abstract

Background: International guidelines on intraductal papillary mucinous neoplasm (IPMN) recommend a formal oncological resection including splenectomy when distal pancreatectomy is indicated. This study aimed to compare oncological and surgical outcomes after distal pancreatectomy with or without splenectomy in patients with presumed IPMN.

Methods: An international, retrospective cohort study was undertaken in 14 high-volume centres from 7 countries including consecutive patients after distal pancreatectomy for IPMN (2005–2019). Patients were divided into spleen-preserving distal pancreatectomy (SPDP) and distal pancreatectomy with splenectomy (DPS). The primary outcome was lymph node metastasis (LNM). Secondary outcomes were overall survival, duration of operation, blood loss, and secondary splenectomy.

Results: Overall, 700 patients were included after distal pancreatectomy for IPMN; 123 underwent SPDP (17.6%) and 577 DPS (82.4%). The rate of malignancy was 29.6% (137 patients) and the overall rate of LNM 6.7% (47 patients). Patients with preoperative suspicion of malignancy had a LNM rate of 17.2% (23 of 134) versus 4.3% (23 of 539) among patients without suspected malignancy ($P < 0.001$). Overall, SPDP was associated with a shorter operating time (median 180 versus 226 min; $P = 0.001$), less blood loss (100 versus 336 ml; $P = 0.001$), and shorter hospital stay (5 versus 8 days; $P < 0.001$). No significant difference in overall survival was observed between SPDP and DPS for IPMN after correction for prognostic factors (HR 0.50, 95% c.i. 0.22 to 1.18; $P = 0.504$).

Conclusion: This international cohort study found LNM in 6.7% of patients undergoing distal pancreatectomy for IPMN. In patients without preoperative suspicion of malignancy, SPDP seemed oncologically safe and was associated with improved short-term outcomes compared with DPS.

Introduction

Pancreatic cystic neoplasms are being detected at an increasing rate because of the expanding use of high-quality cross-sectional imaging^{1,2}. A weighted incidence of incidental pancreatic cysts of up to 49% has been reported in the general population³. The most

common pancreatic cystic neoplasm is intraductal pancreatic mucinous neoplasm (IPMN), for which surveillance is mostly recommended, whereas high-risk patients (for example those with IPMN with mural nodules, jaundice, and main duct dilatation exceeding 10 mm) are recommended to undergo resection to prevent malignant degeneration^{4,5}.

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Distal pancreatectomy is the standard surgical procedure for IPMN located in the pancreatic body and tail requiring resection. In patients with malignant disease (such as pancreatic cancer), distal pancreatectomy is routinely combined with splenectomy to ensure radical resection of potential lymph node metastases (LNMs). At present, both international⁴ and European⁵ guidelines recommend distal pancreatectomy with splenectomy for all patients with IPMN requiring distal pancreatectomy. However, the need for distal pancreatectomy with splenectomy in patients with premalignant IPMN remains unclear because this advice is based on small cohort studies, and a possible survival benefit compared with spleen-preserving distal pancreatectomy has never been proven.

Splenectomy has been associated with an impaired immune response, need for immunization, and a 0.1–8.5% risk of a potentially lethal overwhelming postsplenectomy infection (OPSI)⁶. Furthermore, long-term follow-up studies in American veterans^{7,8} have shown an increased risk of death from pneumonia, ischaemic heart disease, septicaemia, pulmonary embolism, and different types of cancer, even more than 10 years after splenectomy. Patients with resected IPMN have an excellent prognosis (pooled 5-year survival rate 93.6% in 2868 patients)⁹ and could therefore benefit from spleen preservation. In general, spleen-preserving distal pancreatectomy has been associated with less blood loss, shorter hospital stay and improved long-term health outcomes compared with distal pancreatectomy with splenectomy^{10,11}.

This study aimed to assess the oncological and surgical outcomes of spleen-preserving distal pancreatectomy and distal pancreatectomy with splenectomy in patients with presumed IPMN with and without suspected malignancy in a large, international, multicentre cohort. The primary outcome was the rate of LNM. Secondary outcomes included overall survival (OS), duration of operation, estimated blood loss, and need for secondary splenectomy.

Methods

Study design

This was an international, multicentre retrospective cohort study that included centres participating in the Verona Evidence Based Medicine (EBM) 2020 IPMN consortium. The present manuscript was redacted and drafted under the auspices of this consortium¹². Patients were included from 14 high-volume centres (defined by at least 15 distal pancreatectomies per year for all indications) in 7 countries, which all performed distal pancreatectomy with splenectomy and spleen-preserving distal pancreatectomy. This study was conducted in accordance with the STROBE guidelines for reporting observational studies¹³. The study protocol was approved by the institutional review board of Amsterdam UMC and the requirement to obtain informed consent was waived. All participating institutions followed local regulations regarding study approval and informed consent procedures.

Study population

Consecutive patients who had undergone distal pancreatectomy, either spleen-preserving distal pancreatectomy or distal pancreatectomy with splenectomy, for presumed IPMN between 1 January 2005 and 31 December 2019 were eligible for inclusion. For spleen-preserving distal pancreatectomy, both the Warshaw procedure (splenic vessel resecting)¹⁴ and the Kimura procedure (splenic vessel preserving)¹⁵ were included. Planned

distal pancreatectomy with splenectomy included patients in whom splenectomy was planned before operation, thereby excluding emergency splenectomies. Patients were excluded if essential information was lacking (surgical or pathology reports missing) or if pancreatic resections other than distal pancreatectomy were performed. The diagnosis of IPMN was based on the preoperative assessment by the local multidisciplinary team. Subgroup analyses were undertaken for patients with and without preoperative suspicion of malignancy. Patients were classified as having suspected malignancy if there was preoperative suspicion of a solid mass, cytology showing malignancy, or lymphadenopathy on preoperative imaging. All other patients were classified as not having a suspected malignancy, regardless of the postoperative dysplasia grade. Patients in whom the indication for resection was unknown were omitted from these subgroup analyses.

Data collection

Invitations to participate in the present study were distributed via e-mail through the EBM 2020 on IPMN consortium. After an initial participation survey (Google™ Survey, Mountain View, CA, USA) confirming the study requirements, each participating centre appointed one dedicated local study coordinator, who was responsible for all communication with the central study coordinator. The local study coordinator was responsible for data entry into the electronic case report form using Castor EDC¹⁶. An overview of the variables collected is available in [Table S1](#).

Outcomes

The primary outcome was the rate of LNM, both overall and in patients with and those without suspected malignancy. Secondary outcomes included duration of operation, estimated blood loss, 90-day pancreas-specific complications, major in-hospital morbidity (Clavien–Dindo grade IIIa or higher)¹⁷, long-term postoperative morbidity (new-onset diabetes mellitus, exocrine pancreatic insufficiency, and secondary splenectomy), and OS. OS was defined as the interval between the date of surgery and date of death or last follow-up. The definitions of the International Study Group on Pancreatic Surgery were used to score postoperative pancreatic fistula¹⁸, delayed gastric emptying¹⁹, chyle leak²⁰, and postpancreatectomy haemorrhage²¹. Only grade B/C complications were included. Ischaemic morbidity was defined as an abdominal organ complication caused by surgery-related ischaemia. Lymph node stations were reported according to the Japanese classification of pancreatic cancer²². Disease staging was carried out according to the seventh version of the AJCC TNM classification²³ until 2017; the eighth version of the AJCC²⁴ was used from 2018 onwards.

Statistical analysis

Categorical data are presented as numbers with percentages, and were analysed using the χ^2 test or Fisher's exact test, if appropriate. Continuous data are presented as median (i.q.r.) and were compared using the Mann–Whitney *U* test. OS was calculated using the Kaplan–Meier method and analysed using the log rank test.

All *P* values were based on a two-sided test and *P* < 0.050 was considered statistically significant. Data were analysed with the use of SPSS® Statistics for Windows® version 26.0 (IBM, Armonk, NY, USA).

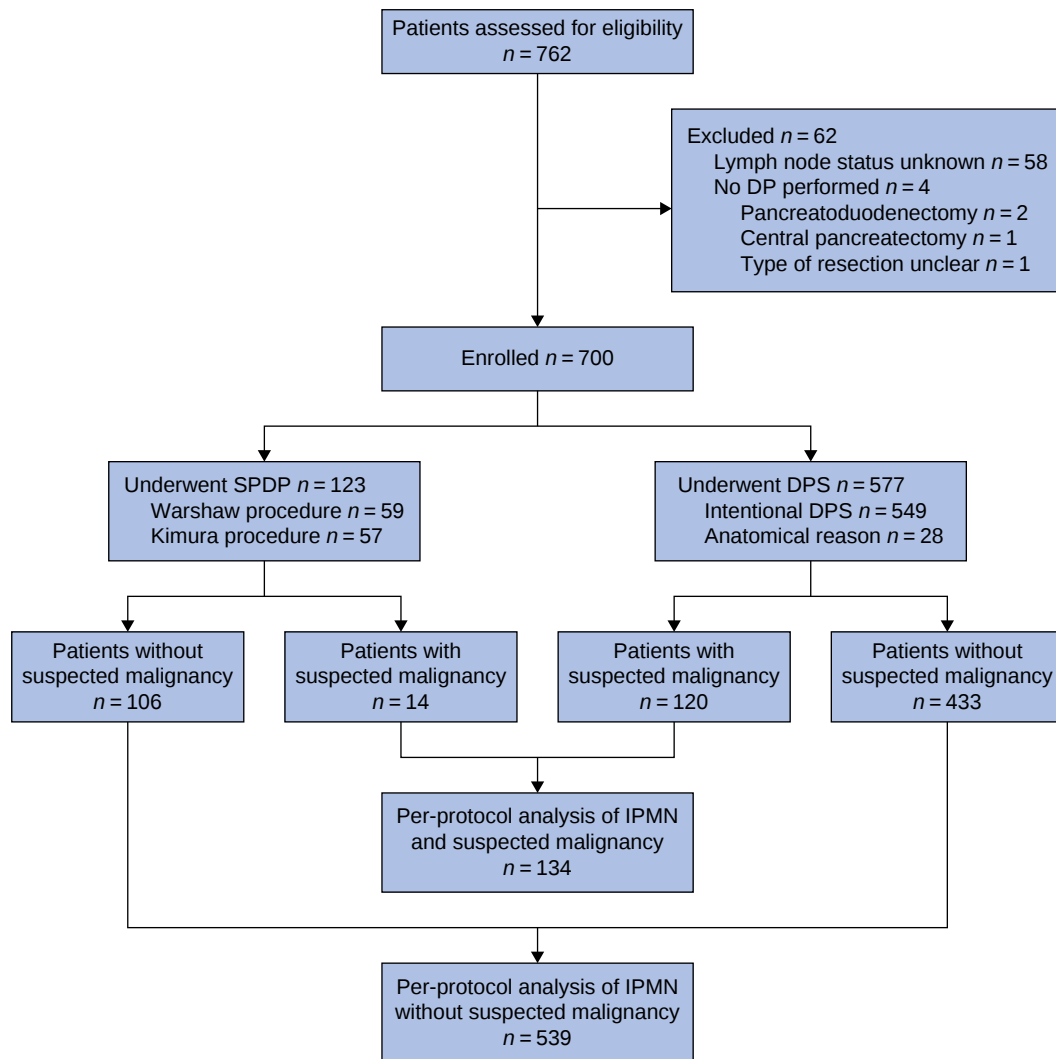


Fig. 1 Study flow chart

DP, distal pancreatectomy; SPDP, spleen-preserving distal pancreatectomy; DPS, distal pancreatectomy with splenectomy; IPMN, intraductal papillary mucinous neoplasm.

Results

Overall, 700 patients were included, of whom 123 (17.6%) had undergone spleen-preserving distal pancreatectomy and 577 (82.4%) distal pancreatectomy with splenectomy (Fig. 1). The majority of these patients underwent planned splenectomy (549 patients, 95.1%). Spleen-preserving distal pancreatectomy was performed by the Warshaw procedure in 59 patients (48.0%) and the Kimura procedure in 57 (46.3%); the procedure type was unknown for 7 patients (5.7%). All but one hospital performed both spleen-preserving distal pancreatectomy and distal pancreatectomy with splenectomy, and one hospital performed only distal pancreatectomy with splenectomy. One hospital carried out more spleen-preserving distal pancreatectomies than distal pancreatectomies with splenectomy. The cohort had a median age of 70 (i.q.r. 63–76) years and 344 patients (49.1%) were men. Patients undergoing spleen-preserving distal pancreatectomy were younger (68 (61–74) versus 70 (63–76) years; $P=0.003$) (Table 1). The most common indication for resection was a dilated main pancreatic duct, which was present in 329 patients (47.0%) in the total cohort. An overview of all indications for resection is available in Table S2. Most patients

were diagnosed with low-grade dysplasia (242, 34.6%), whereas 165 (23.6%) had intermediate-grade dysplasia, 120 (17.1%) had high-grade dysplasia, and 137 (19.6%) had invasive cancer in IPMN. In the total cohort, a median of 11 (i.q.r. 5–20) lymph nodes were harvested per patient and 47 patients (6.7%) had LNM.

Per-protocol analysis

In the per-protocol analysis of the subgroup of 134 patients with IPMN and suspected malignancy, 74 (55.2%) were diagnosed with invasive cancer. This included 4 of 14 patients (29%) after spleen-preserving distal pancreatectomy and 70 of 120 (58.3%) after distal pancreatectomy with splenectomy ($P=0.104$ overall) (Table S3). LNMs were found in 1 of 14 patients (7%) after spleen-preserving distal pancreatectomy and 22 of 120 (18.3%) after distal pancreatectomy with splenectomy (relative risk (RR) 0.39, 95% c.i. 0.06 to 2.67; $P=0.463$).

In the per-protocol analysis of the subgroup of 539 patients without suspected malignancy, 61 patients (11.3%) were diagnosed with invasive cancer. These included 5 patients (5%) after spleen-preserving distal pancreatectomy and 56 (13%) after distal pancreatectomy with splenectomy ($P<0.001$ overall).

Table 1 Baseline characteristics of 700 patients after distal pancreatectomy for suspected intraductal papillary mucinous neoplasm

	SPDP (n = 123)	DPS (n = 577)	P‡
Sex			0.494
Male	57 (46.3)	287 (49.7)	
Female	66 (53.7)	290 (50.3)	
Age (years), median (i.q.r.)	68 (61–74)	70 (63–76)	0.003§
WHO performance status			0.981
0–1	104 (84.5)	481 (83.4)	
2–4	9 (7.3)	42 (7.3)	
Missing	10 (8.1)	54 (9.4)	
ASA fitness grade			0.243
I–II	95 (77.2)	400 (69.3)	
III–IV	28 (22.7)	155 (26.9)	
Missing	0 (0)	22 (3.8)	
History of pancreatitis	22 (17.9)	99 (17.2)	0.853
Co-morbidities	95 (77.2)	428 (74.2)	0.479
Cardiac	34 (27.6)	138 (23.9)	
Vascular	28 (22.7)	184 (31.9)	
Diabetes	15 (12.2)	128 (22.2)	
Pulmonary	11 (8.9)	57 (9.9)	
Neurological	4 (3.2)	18 (3.1)	
Gastrointestinal	31 (25.2)	78 (13.5)	
Urogenital	5 (4.1)	15 (2.6)	
Renal	6 (4.9)	26 (4.5)	
Connective tissue disease	0 (0)	6 (1.0)	
Immunological	3 (2.4)	14 (2.4)	
Oncological	23 (18.7)	75 (13.0)	
Other	5 (4.1)*	13 (2.2)†	

Values are n (%) unless otherwise indicated. Other co-morbidities included *hyperthyroidism (2), hypothyroidism (2), and haemochromatosis (1); †hyperthyroidism (1), hypothyroidism (8), gout (2), Cushing syndrome (1), and Addison disease (1). SPDP, spleen-preserving distal pancreatectomy; DPS, distal pancreatectomy with splenectomy. ‡ χ^2 test or Fisher's exact test, except §Mann-Whitney U test.

(Table 2). Fewer lymph nodes were harvested in patients undergoing spleen-preserving distal pancreatectomy (median 4 (i.q.r. 1–7) versus 12 (5–20); $P < 0.001$). In total, LNMs were found in 23 of 539 patients (4.3%). Among those without suspected malignancy, LNMs were found in 1 of 106 patients (0.9%) who had spleen-preserving distal pancreatectomy, compared with 22 of 433 (5.1%) after distal pancreatectomy with splenectomy (RR 0.19, 0.03 to 1.36; $P = 0.062$).

Intention-to-treat analysis

Intention-to-treat analysis of the subgroup of patients with a preoperative suspicion of malignancy yielded comparable results (Table S4). In intention-to-treat analysis of patients without suspected malignancy, similar results were observed (Table S5).

Surgical outcomes

In the overall cohort, spleen-preserving distal pancreatectomy was more frequently performed with the use of minimally invasive surgery (59 of 123, 48.0%) than distal pancreatectomy with splenectomy (162 of 577, 28.1%) ($P < 0.001$) (Table S6). Operating time was 46 min shorter in patients undergoing spleen-preserving distal pancreatectomy (median 180 (i.q.r. 120–241) versus 226 (162–280) min; $P = 0.001$), and blood loss was 236 ml less with spleen preservation (100 (50–250) versus 336 (100–383) ml; $P = 0.001$). Hospital stay was 3 days shorter in patients who underwent spleen-preserving distal pancreatectomy (median 5 (i.q.r. 4–7) versus 8 (6–14) days). None of the patients needed a secondary splenectomy after an initial spleen-preserving distal pancreatectomy. There was no difference in adverse events

Table 2 Pathological outcome and lymph node metastases in the per-protocol analysis of 539 patients with intraductal papillary mucinous neoplasm after distal pancreatectomy without preoperative suspicion of malignancy

	SPDP (n = 106)	DPS (n = 433)	Relative risk*	P‡
Grade of dysplasia			–	< 0.001§
Low	57 (53.8)	150 (34.6)		
Intermediate	24 (22.6)	123 (28.4)		
High	12 (11.3)	88 (20.3)		
Invasive cancer	5 (4.7)	56 (12.9)		
Not reported	8 (7.5)	16 (3.7)		
No. of lymph nodes harvested, median (i.q.r.)	4 (1–7)	12 (5–20)	–	< 0.001¶
No. of patients with positive lymph nodes	1 of 106 (0.9)	22 of 433 (5.1)	0.19 (0.03, 1.36)	0.062
Nodule or enhancing wall	1 of 19 (5)	5 of 97 (5)	1.02 (0.13, 8.26)	> 0.99
Main duct involvement	0 of 43 (0)	10 of 184 (5)	–	0.215
Growth or cyst size	0 of 37 (0)	5 of 104 (5)	–	0.326
Increased CA19.9 level	0 of 1 (0)	1 of 6 (17)	–	> 0.99
Clinical symptoms†	0 of 4 (0)	0 of 6 (0)	–	–
Other indication	0 of 2 (0)	1 of 12 (8)	–	> 0.99

Values are n (%) unless otherwise indicated; *values in parentheses are 95% confidence intervals. †New onset or worsening of pre-existing diabetes mellitus, pancreatitis, or persisting abdominal symptoms. SPDP, spleen-preserving distal pancreatectomy; DPS, distal pancreatectomy with splenectomy; CA19.9, carbohydrate antigen 19.9. ‡Fisher's exact test, except § χ^2 test and ¶Mann-Whitney U test.

after spleen-preserving distal pancreatectomy versus distal pancreatectomy with splenectomy. New-onset diabetes mellitus occurred in 175 patients (25.0%) and exocrine pancreatic insufficiency in 114 (16.3%).

Overall survival

After a median follow-up of 52 months, 115 of 700 patients (16.4%) had died. Mean estimated survival time was better after spleen-preserving distal pancreatectomy (154 (95% c.i. 144 to 164) months) than after distal pancreatectomy with splenectomy (145 (137 to 153) months) ($P = 0.005$). The 1-, 3- and 5-year estimated survival rates were, respectively, 99, 97, and 95% in patients with low-grade dysplasia, 96, 92, and 89% for those with intermediate-grade dysplasia, and 96, 89, and 77% for patients with high-grade dysplasia. Estimated survival rates for those with invasive cancers were 87% after 1 year, 66% after 3 years, and 53% after 5 years.

Among patients without suspected malignancy, a total of 73 of 539 (13.5%) had died after a median follow-up of 55 months. Of these, 7 (7%) died after spleen-preserving distal pancreatectomy versus 66 (15%) after distal pancreatectomy with splenectomy. Mean estimated OS was better after spleen-preserving distal pancreatectomy (158 (148 to 167) versus 152 (143 to 160) months; $P = 0.017$) (Fig. 2). However, the association between spleen-preserving distal pancreatectomy and OS did not remain after correction for dysplasia grade (HR 0.48, 95% c.i. 0.29 to 1.11; $P = 0.085$) (Fig. S1). The result was similar when both dysplasia grade and age were corrected for in multivariable analysis (HR 0.50, 0.22 to 1.18; $P = 0.504$) (Table 3). Factors associated with worse OS were age (HR 1.95, 1.20 to 3.12;

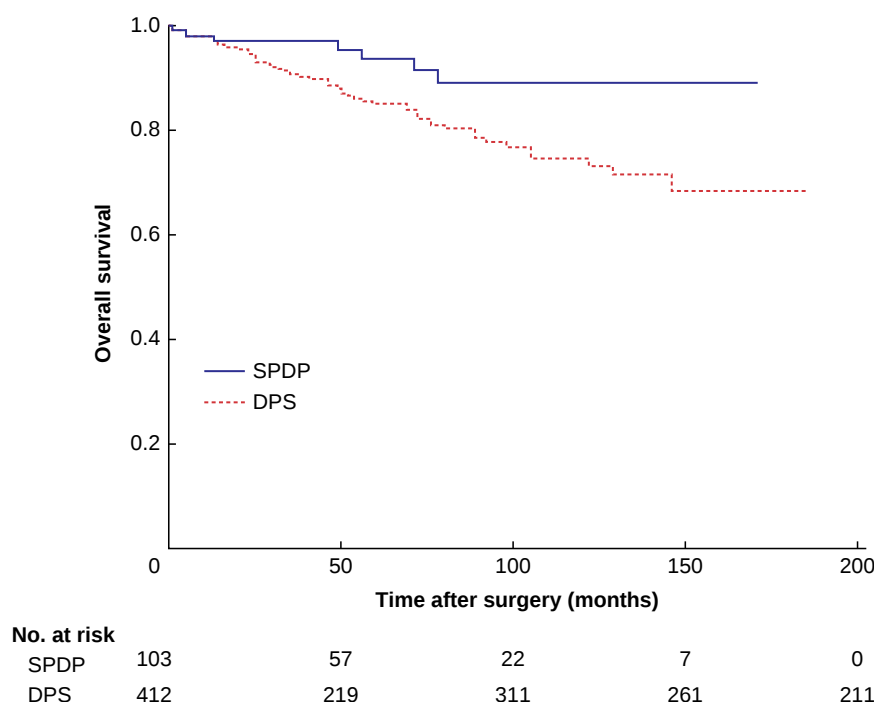


Fig. 2 Kaplan-Meier estimates of overall survival after spleen-preserving distal pancreatectomy versus distal pancreatectomy with splenectomy in patients without suspected malignancy

SPDP, spleen-preserving distal pancreatectomy; DPS, distal pancreatectomy with splenectomy.

Table 3 Cox regression analyses evaluating predictors of overall survival in patients without suspected malignancy

	Univariate analysis		Multivariable analysis	
	HR	P	HR	P
Age > 70 years	1.96 (1.22, 3.25)	0.006	1.95 (1.20, 3.12)	0.007
SPDP	0.41 (0.21, 0.79)	0.007	0.50 (0.22, 1.18)	0.504
Nodule or enhancing wall	1.44 (0.86, 2.43)	0.165	–	–
Main duct involvement	0.75 (0.46, 1.23)	0.251	–	–
Growth or cyst size	0.95 (0.56, 1.61)	0.847	–	–
Increased CA19.9 level	1.17 (0.16, 8.46)	0.873	–	–
Clinical symptoms*	0.46 (0.06, 3.32)	0.441	–	–
Grade of dysplasia				
Low	1.00 (reference)		1.00 (reference)	
Intermediate	2.04 (0.98, 4.27)	0.058	1.94 (0.93, 4.07)	0.078
High	3.20 (1.51, 6.78)	0.002	2.96 (1.39, 6.29)	0.005
Invasive	9.41 (4.54, 19.50)	< 0.001	8.26 (3.95, 17.27)	< 0.001

Values in parentheses are 95% confidence intervals. *New onset or worsening of pre-existing diabetes mellitus, pancreatitis, or persisting abdominal symptoms. SPDP, spleen-preserving distal pancreatectomy; CA19.9, carbohydrate antigen 19.9.

$P = 0.007$), high-grade dysplasia (HR 2.96, 1.39 to 6.29; $P = 0.005$), and invasive cancer (HR 8.26, 3.95 to 17.27; $P < 0.001$).

Discussion

In this first international cohort study of the role of splenectomy in patients undergoing distal pancreatectomy for IPMN, the LNM rate was 6.7% in the total cohort and 4.3% among patients without a preoperative suspicion of malignancy. Spleen-preserving distal pancreatectomy was associated with a shorter operating time, shorter hospital stay, and less blood loss than distal pancreatectomy with splenectomy, and comparable OS.

The 6.7% rate of LNM after distal pancreatectomy observed here cannot be compared with findings of previous studies as these

combined all types of pancreatectomy for IPMN. In a single-year analysis²⁵ in over 100 US centres, 21 patients (4.4%) had LNM among 478 patients after any type of pancreatectomy for IPMN. A single-centre series²⁶ from Johns Hopkins identified 183 patients (29.7%) with malignancy and 97 (15.7%) with LNM among 616 patients undergoing any type of pancreatectomy for IPMN. Two smaller single-centre studies^{27,28} reported LNM in 7 of 98 (7%) and 27 of 244 (11.1%) patients undergoing any type of pancreatectomy for IPMN respectively.

The main benefit of spleen-preserving distal pancreatectomy is improvement in short-term outcome and preservation of splenic function, which may be considered especially important as most patients with IPMN have a very good life expectancy; however, the proportion of minimally invasive operations was higher in the

spleen-preserving distal pancreatectomy group (Table S6), and so the results should be interpreted with caution. A 2014 meta-analysis¹⁰ compared outcomes after spleen-preserving distal pancreatectomy and distal pancreatectomy with splenectomy in 879 patients for all indications, and concluded that spleen-preserving distal pancreatectomy was associated with a shorter hospital stay (weighted mean difference 1.16, 95% c.i. -2.00 to -0.31; $P=0.007$) and fewer intra-abdominal abscesses (OR 0.48, 0.27 to 0.83; $P=0.009$), whereas other outcomes did not differ (such as blood loss and duration of operation). A more recent study²⁹ reported high success rates (80%) for laparoscopic spleen-preserving distal pancreatectomy in 229 patients with benign and low-grade malignant disease, with no differences in postoperative morbidity in propensity score-matched patients, compared with 227 patients who underwent distal pancreatectomy with splenectomy. The authors concluded that spleen-preserving distal pancreatectomy is preferred for benign or low-grade malignant lesions owing to the increased risk of long-term complications after distal pancreatectomy with splenectomy. Another recent study³⁰ of propensity score-matched patients (35 in each group) undergoing distal pancreatectomy for all indications found that the operating time was shorter for laparoscopic spleen-preserving distal pancreatectomy than for laparoscopic distal pancreatectomy with splenectomy. Furthermore, the authors noted higher quality-of-life (QoL) scores after spleen-preserving distal pancreatectomy, albeit the difference was not statistically significant. A follow-up study³¹ of 160 patients with benign or low-grade malignant disease reported improved QoL (less fatigue, symptoms of flu and cold, and better health condition) after spleen-preserving distal pancreatectomy *versus* distal pancreatectomy with splenectomy.

A possible disadvantage of spleen-preserving distal pancreatectomy is the risk of splenic infarction and splenic abscesses. Splenic infarction requiring reoperation was not observed in the present cohort, but other studies reported incidences ranging from 1.9 to 7.3%^{31–33}. Long-term complications after spleen-preserving distal pancreatectomy according to Warshaw include left-sided portal hypertension and subsequent formation of epigastric varices. Unfortunately, these were not registered in the authors' database and so it was not possible to provide data on this complication. Two of the aforementioned studies^{31,32} with long-term follow-up reported a 9 and 25% risk of varices after spleen-preserving distal pancreatectomy according to Warshaw in 65 and 111 patients respectively, although no significant gastrointestinal bleeding was observed.

Focusing on OS, the good life expectancy (90% after a median follow-up of 4.6 years) observed here is in accordance with a systematic review⁹ from 2016, in which the pooled 5-year survival rate in 2868 patients was 93.6% (95% c.i. 90.5 to 95.7). A more recently published abstract³⁴ with 10-year nationwide follow-up of 88 resections (all types) for IPMN reported a 5-year survival rate of 87.5% for patients with low-grade dysplasia, 77.8% for those with high-grade dysplasia, and 35.9% for patients with invasive IPMN.

The present data suggest that spleen-preserving distal pancreatectomy was safe in patients with IPMN without preoperative suspicion of malignancy selected for this approach. According to the current policies for IPMN resection, most resected IPMNs do not harbour either high-grade dysplasia or invasive cancer^{35,36}. Ultimately, a large pragmatic randomized trial should confirm the non-inferiority of spleen-preserving distal pancreatectomy to distal pancreatectomy with splenectomy for patients with IPMN without suspected malignancy. Such a study should include long-term follow-up to

create insight into the long-term complications of both spleen-preserving distal pancreatectomy (for example varices) and distal pancreatectomy with splenectomy (such as OPSI), and should also include QoL questionnaires. In addition, standardization of lymph node station reporting is needed to distinguish LNM accurately. If the results of these future studies show that spleen-preserving distal pancreatectomy has significant benefit over distal pancreatectomy with splenectomy in patients with IPMN, spleen-preserving distal pancreatectomy might be implemented in clinical practice, thus potentially improving surgical outcomes and QoL. In the present study, 5 of 106 patients had invasive cancer in the spleen-preserving distal pancreatectomy group but none underwent secondary splenectomy. The clinical consideration remains open for debate whether a secondary splenectomy should be performed.

The results of this study should be interpreted considering several limitations. First, owing to the retrospective design, the results are subject to indication bias. This is reflected by the higher dysplasia grade and higher rate of LNM in patients undergoing distal pancreatectomy with splenectomy for IPMN, indicating that patients with higher preoperative risk were specifically selected for distal pancreatectomy with splenectomy. Nevertheless, this was corrected for in Cox regression analyses. Second, it was not possible to provide detailed data on the location of LNMs (splenic hilum *versus* elsewhere) because this information was not present in most pathology reports. Additionally, stage migration might have taken place as a median of 11 (i.q.r. 5–20) lymph nodes were harvested per patient. Third, long-term follow-up was lacking in some patients, and the reliability of detection of the consequences of spleen-preserving distal pancreatectomy and distal pancreatectomy with splenectomy (for example OPSI) might therefore have been impaired. Fourth, data were not collected on IPMN recurrence. Fifth, the inclusion period of 15 years might have led to confounding because guidelines have changed over this interval, pancreatic cystic neoplasms are increasingly being diagnosed, and use of the minimally invasive approach has increased. The main strength of this study is its multicentre, international design with a considerable cohort of patients undergoing distal pancreatectomy for presumed IPMN. This study is also the first to provide insight into OS between patients undergoing spleen-preserving and those having distal pancreatectomy with splenectomy for IPMN. A future pragmatic randomized trial should confirm the non-inferiority of spleen-preserving distal pancreatectomy compared with distal pancreatectomy with splenectomy in patients requiring distal pancreatectomy for presumed IPMN without suspected malignancy.

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Disclosure

J.E.v.H. currently has a role as independent observer for Olympus and has received honoraria from Cook Medical, Boston Scientific, Metronic, and Abbvie. The authors declare no other conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The data sets generated during and/or analysed during this study are not publicly available, but are available from the corresponding author on reasonable request.

References

- Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. *J Am Coll Radiol* 2010;**7**:754–773
- van Huijgevoort NCM, Del Chiaro M, Wolfgang CL, van Hooft JE, Besselink MG. Diagnosis and management of pancreatic cystic neoplasms: current evidence and guidelines. *Nat Rev Gastroenterol Hepatol* 2019;**16**:676–689
- Kromrey ML, Bulow R, Hubner J, Paperlein C, Lerch MM, Ittermann T et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 2018;**67**:138–115
- Tanaka M, Fernandez-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatol* 2017;**17**:738–753
- European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 2018;**67**:789–804
- Casciani F, Trudeau MT, Vollmer CM Jr. Perioperative immunization for splenectomy and the surgeon's responsibility: a review. *JAMA Surg* 2020;**155**:1068–1077
- Robinette CD, Fraumeni JF Jr. Splenectomy and subsequent mortality in veterans of the 1939–45 war. *Lancet* 1977;**2**:127–129
- Kristinsson SY, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica* 2014;**99**:392–398
- Mizrahi M, Bartley A, Cohen J, Grunwald D, Tseng JF, Sheridan J et al. Survival after resection of pancreatic intraductal papillary mucinous neoplasms: a systematic review and meta-analysis. *Gastroenterology* 2016;**150**:S651
- He Z, Qian D, Hua J, Gong J, Lin S, Song Z. Clinical comparison of distal pancreatectomy with or without splenectomy: a meta-analysis. *PLoS One* 2014;**9**:e91593
- Tang CW, Feng WM, Bao Y, Fei MY, Tao YL. Spleen-preserving distal pancreatectomy or distal pancreatectomy with splenectomy?: perioperative and patient-reported outcome analysis. *J Clin Gastroenterol* 2014;**48**:e62–e66
- Verona EBM 2020 on IPMN Consortium. Verona Evidence-Based Meeting (EBM) 2020 on intraductal papillary mucinous neoplasms (IPMNs) of the pancreas: meeting report. *Dig Surg* 2021;**38**:316–322
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP et al. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–1457
- Warshaw AL. Conservation of the spleen with distal pancreatectomy. *Arch Surg* 1988;**123**:550–553

15. Kimura W, Inoue T, Futakawa N, Shinkai H, Han I, Muto T. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. *Surgery* 1996;**120**:885–890
16. Castor. *Castor Electronic Data Capture*. <https://castoredc.com> (accessed 19 September 2022)
17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**:205–213
18. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017;**161**:584–591
19. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007;**142**:761–768
20. Besselink MG, van Rijssen LB, Bassi C, Dervenis C, Montorsi M, Adham M et al. Definition and classification of chyle leak after pancreatic operation: a consensus statement by the International Study Group on Pancreatic Surgery. *Surgery* 2017;**161**:365–372
21. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007;**142**:20–25
22. Isaji S, Murata Y, Kishiwada M, Neoptolemos J, Urrutia R, Abbruzzese J et al. *Pancreatic Cancer*. In: Neoptolemos J, Urrutia R, Abbruzzese J, Büchler M (ed.), New York: Springer, 2018, 1021–1037
23. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;**17**:1471–1474
24. Chun YS, Pawlik TM, Vauthey JN. 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. *Ann Surg Oncol* 2018;**25**:845–847
25. Khoury RE, Kabir C, Maker VK, Banulescu M, Wasserman M, Maker AV. What is the incidence of malignancy in resected intraductal papillary mucinous neoplasms? An analysis of over 100 US institutions in a single year. *Ann Surg Oncol* 2018;**25**:1746–1751
26. Rezaee N, Barbon C, Zaki A, He J, Salman B, Hruban RH et al. Intraductal papillary mucinous neoplasm (IPMN) with high-grade dysplasia is a risk factor for the subsequent development of pancreatic ductal adenocarcinoma. *HPB (Oxford)* 2016;**18**:236–246
27. Kimura K, Amano R, Ymazoe S, Ohira G, Nishio K, Hirakawa K et al. The clinical indications for limited surgery of intraductal papillary mucinous neoplasms of the pancreas. *World J Surg* 2017;**41**:1358–1365
28. Imaizumi T, Hatori T, Harada N, Fukuda A, Takasaki K, Hanyu F. Intraductal papillary mucinous neoplasm of the pancreas; resection and cancer prevention. *Am J Surg* 2007;**194**:S95–S99
29. Moekotte AL, Lof S, White SA, Marudanayagam R, Al-Sarireh B, Rahman S et al. Splenic preservation versus splenectomy in laparoscopic distal pancreatectomy: a propensity score-matched study. *Surg Endosc* 2020;**34**:1301–1309
30. Zhang RC, Ma J, Mou YP, Yan JF, Zhou YC. Comparison of clinical outcomes and quality of life between laparoscopic distal pancreatectomy with or without spleen preservation. *Surg Endosc* 2021;**35**:3412–3420
31. Ferrone CR, Konstantinidis IT, Sahani DV, Wargo JA, Fernandez-del Castillo C, Warshaw AL. Twenty-three years of the Warshaw operation for distal pancreatectomy with preservation of the spleen. *Ann Surg* 2011;**253**:1136–1119
32. Paiella S, De Pastena M, Korrel M, Pan TL, Butturini G, Nessi C et al. Long term outcome after minimally invasive and open Warshaw and Kimura techniques for spleen-preserving distal pancreatectomy: international multicenter retrospective study. *Eur J Surg Oncol* 2019;**45**:1668–1673
33. Adam JP, Jacquin A, Laurent C, Collet D, Masson B, Fernández-Cruz L et al. Laparoscopic spleen-preserving distal pancreatectomy: splenic vessel preservation compared with the Warshaw technique. *JAMA Surg* 2013;**148**:246–252
34. Vaalavuo Y, Vornanen M, Antila A, Ahola R, Rinta-Kiikka I, Sand J et al. Ten-year nationwide survival of operated IPMNs. *Pancreas* 2021;**50**:1105
35. Marchegiani G, Andrianello S, Morbin G, Secchettin E, D'Onofrio M, De Robertis R et al. Importance of main pancreatic duct dilatation in IPMN undergoing surveillance. *Br J Surg* 2018;**105**:1825–1834
36. Marchegiani G, Pollini T, Andrianello S, Tomasoni G, Biancotto M, Javed AA et al. Progression vs cyst stability of branch-duct intraductal papillary mucinous neoplasms after observation and surgery. *JAMA Surg* 2021;**156**:654–661