European Journal of Surgical Oncology 45 (2019) 1668–1673

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Consensus Statement

Long term outcome after minimally invasive and open Warshaw and Kimura techniques for spleen-preserving distal pancreatectomy: International multicenter retrospective study☆

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A R T I C L E I N F O

Article history:
Received 12 February 2019
Received in revised form
27 March 2019
Accepted 3 April 2019
Available online 8 April 2019

Keywords:
Parenchyma-sparing pancreatic resection
Spleen-preserving pancreatectomy
Pancreatic neuroendocrine tumor
Minimally invasive pancreatic resection
Pancreatic resection

A B S T R A C T

Background: The Warshaw (WT) and the Kimura (KT) techniques are both used for open or minimally invasive (MI) spleen preserving distal pancreatectomy (SPDP). Multicenter studies on long-term outcome of WT and KT are lacking.

Methods: Multicenter retrospective study with transversal follow-up moment, including patients who underwent SPDP from 2000 to 2017 at three high-volume centers in Italy and the Netherlands. Primary endpoint was the incidence of short and long term complications. Patients without regular follow-up were interviewed about symptoms and complications.

Results: In total, 164 patients were enrolled, 55 WT (33.5%) and 109 kT (66.5%), of which 95 (57.9%) MI. There was no 30-day mortality (0%).The only significant difference in short-term outcome was more delayed gastric emptying (DGE) after WT (9.1% vs 1.8%, $p = 0.043$). MI-SPDP was associated with less blood loss (median 150 vs 250 ml, respectively, $p < 0.001$), less DGE (0% vs 10%, $p = 0.002$), less abdominal abscesses (8.4% vs 18.4%, $p = 0.03$) and less splenic infarctions (3.2% vs. 13%, $p = 0.042$), than open SPDP. Long-term follow-up (median 41 months) was available for 111 patients (67.7%) of whom 18 (16.2%) had an SPDP-related long-term sequela, mostly perigastric varices ($n = 11$, 9%) but without differences between WT and KT. Less long-term sequelae were reported after MI as compared to open SPDP (12.5% vs 21.2%, $p = 0.032$).

Conclusions: In this international retrospective study, the WT and KT had comparable short- and long-term outcomes. If a KT does not seem feasible during SPDP, a WT is recommended, rather than performing a splenectomy. MI-SPDP was associated with less short- and long term complications as compared to an open SPDP.

1. Introduction

Distal pancreatectomy with splenectomy is the treatment of choice for cancers in the pancreatic body and tail. Splenectomy is performed for two reasons: (1) oncological; it is mandatory to perform an adequate lymphadenectomy [station #10 of the Japan Pancreas Society [1,2]] and (2) technique; when removing tumors very close to the splenic hilum. When patients have non-malignant

☆ This work was initially presented at the APA/IAP joint congress (Miami, USA, October 31st - November 3rd, 2018) and at the HPBSurG Meeting (Lyon, France, November 15th-16th, 2018).

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https://doi.org/10.1016/j.ejso.2019.04.004

disease, spleen preserving distal pancreatectomy (SPDP) should be considered, as several types of middle/long-term post-splenectomy complications such as abdominal abscesses, thrombocytosis, pulmonary hypertension, venous and arterial thrombosis, and overwhelming post-splenectomy infections (OPSI) have been described after splenectomy [3,4]. Furthermore, all splenectomized patients should be vaccinated against pneumococcus, haemophilus influenzae type-b and meningococcus at additional costs to the national health system and this patients still have a small risk of OPSI. Some countries (e.g. the Netherlands) even advice two years of prophylactic antibiotics after splenectomy [5]. Probably on the basis of these pathophysiological theoretical advantages, the preliminary results of a worldwide survey demonstrated that 60% of pancreatic surgeons consider spleen preservation during distal pancreatectomy 'moderately to markedly advantageous' [6].

To date, three meta-analyses of non-randomized studies compared the clinical outcomes of distal pancreatectomy with splenectomy and SPDP [7–9]. These reports suggest that SPDP is associated with lower rates of postoperative complications, especially infectious.

The indications for SPDP include pancreatic tumors that do not require a lymphadenectomy or an extensive retroperitoneal clearance. These situations include selected neuroendocrine tumors [10], serous and mucinous cystadenomas and, in some cases, intraductal papillary mucinous neoplasms without clear signs of malignant degeneration.

SPDP can be carried out in two different ways: with splenic vessels preservation (called the Kimura technique [KT]) [11] and splenic vessels resection (called the Warshaw technique [WT] [12]. Some surgeons have expressed concerns about the WT and would rather perform a splenectomy if the KT is not feasible. On the one hand, the reduced blood flow to the spleen may after WT lead to splenic infarctions with possible subsequent splenectomy; on the other hand, an increased blood flow through the short gastric veins may be responsible for gastric varices and with a (small) risk of gastric variceal bleeding. Recent meta-analyses agree in finding a higher incidence rate of splenic infarction and subsequent splenectomy in the WT group but randomized studies and large international studies are lacking [7,13–17]. Both procedures can be done minimally invasive (MI) or open. A recent first randomized controlled trial confirmed that minimally invasive distal pancreatectomy is associated with superior outcomes [18].

Therefore, this study was designed to address three issues; First, to assess the long-term clinical and radiological outcomes of WT and KT; Second, to assess differences in postoperative complications between WT and KT; Third, to compare outcomes after MI and open SPDP.

Methods

Patients and design

Patients undergoing SPDP at three high-volume centers in Italy and the Netherlands from 2000 to 2016 were retrospectively analyzed. The internal review boards of the three centers approved this study. Patients were divided into two groups based on the type of SPDP performed: (1) WT or (2) KT. Demographic, pathological, surgical, and postoperative data were collected and compared.

Definitions

The definitions of postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE) and post-pancreatectomy hemorrhage (PPH) were based on the most recent International Study Group on Pancreatic Surgery (ISGPS) guidelines [19–21]. Splenomegaly was defined according to the formula proposed by Prassopoulos et al. [22]. The Clavien-Dindo system [23] was adopted to describe the severity of complications.

Operative techniques and surgical outcomes

WT or KT was performed at the discretion of each surgeon. The two techniques were performed as previously described [11,12]. The procedures were performed either MI or open. For MI we both laparoscopic- and robot-assisted procedures. Converted procedures were analyzed in the MI group.

Data collection

Three prospectively maintained database were queried for patients submitted to SPDP during the study period. Baseline variables collected included age, sex, ASA score, BMI, tumor size at final pathology, diagnosis. Intraoperatively, the surgical approach, the duration of surgery and the estimated blood loss were collected. The following postoperative complications were evaluated within 30 days of surgery: POPF, DGE, PPH, splenic infarct, splenectomy for any surgery-related reason, presence of intra-abdominal abscess requiring drain placement or antibiotic therapy, reintervention, readmission, gastric bleeding and mortality. The length of stay was registered as well.

Follow-up

Patients were contacted directly by phone or at outpatients visits. Considering the long time-period and the almost always benign nature of the underlying disease, patients who were not enrolled in a postoperative follow-up program (for any reason and with any cross-sectional imaging technique) were asked to undergo cross-sectional imaging (contrast-enhanced CT or contrast-enhanced MRI) according to the patient's wishes.

At follow-up patients were asked whether they had: 1) any history of gastrointestinal bleeding; 2) potential spleen-related symptoms (immunological problems, anemia, abdominal left upper quadrant pain, postprandial fullness, need for antiplatelet due to thrombocytosis); 3) any history of splenic rupture; 4) any history of splenectomy; 5) any previous diagnosis of gastric varices; 6) any possible abdominal SPDP-related surgery; 7) the reason for postoperative imaging/follow-up (for those who already underwent imaging); and 8) the postoperative diagnosis of diabetes.

Radiological data were collected with a minimum follow-up of 1 month from surgery and only cross-sectional imaging was considered. For those who already had cross-sectional imaging done for other reasons, a maximum of 12 months after surgery, these scans were included; otherwise imaging was repeated. The presence and timing of the following radiological findings were noted: 1) perigastric varices; 2) splenic infarction; 3) splenomegaly [22]. When the imaging had been performed elsewhere, the scans were reviewed by experienced radiologists in the participating centers.

Statistical analysis

All statistical analyses were performed using SPSS® version 21 (IBM, Armonk, New York, USA). Statistically significant differences were detected using Mann-Whitney U–, Student t-, $\chi 2$ tests with Fisher's test. The long-term time course of post-SPDP sequelae was estimated according to the Kaplan–Meier method and compared univariately with log rank statistics. Statistical significance was set to $P < 0.05$ (2-sided).

Results

Overall, 164 patients were included; 55 (33.5%) patients after WT and 109 (66.5%) after KT, respectively. Table 1 shows the baseline and perioperative characteristics. Overall, an MI approach was used in 95 patients (57.9%) and an open approach in 69 (42.1%). The MI approach was used for WT in 22 (40%) patients and for KT in 73 (66.9%) patients, respectively (p = 0.001). Estimated blood loss was less with MI-SPDP (median (IQR) 150 (135)95%$CI_{median1}$ 132.56–200 vs 250 (553)95%CI_{median} 190–350, respectively, p < 0.001, Mann-Whitney *U* test) and with the KT approach (median (IQR) 160 (150) mL vs 200 (240), p = 0.017, Mann-Whitney *U* test). There was a trends towards a shorter operative time for WT (median (IQR) 181 (82) vs 195 (98) minutes, p = 0.106, Mann-Whitney *U* test). No statistically significant differences were found in the other pre- and intraoperative variables or in the final pathology.

Postoperative outcomes: WT vs. KT

Table 2 shows the postoperative outcomes. DGE was rare (n = 7, 4.3%), slightly more in the WT group (n = 5, 9.1% vs. n = 2. 1.8%, p = 0.043). All other complications did not differ significantly between the groups.

Postoperative outcomes: MI vs. open

MI-SPDP was associated with less DGE (0% vs. 10.1%, p = 0.002), less abdominal abscesses (8.4% vs. 18.8%, p = 0.042) and less splenic infarctions (3.2% vs. 13%, p = 0.03). There was no mortality in both groups.

Long-term outcomes: WT vs. KT

Overall, 111 patients (67.7%) had a clinical and radiological follow-up (median 41 months, IQR 55, 95%CI_{median} 33–48) after surgery. The remaining patients were lost to follow-up (n = 38) or did not accept to be enrolled (n = 15). Radiological follow-up was already available in 86 patients. The reasons for postoperative imaging in these patients were: (1) follow-up of their pancreatic disease (n = 63, 73.3%); (2) abdominal symptoms seemingly unrelated to SPDP (n = 12, 14%); and (3) oncological reasons (n = 11, 12.7%; in 7 and 4 cases the imaging was performed for radiological staging of breast and colon cancer, respectively). The remaining 25 patients underwent cross-sectional imaging for this study as follow-up of their pancreatic disease (9 contrast enhanced MRI and 16 contrast-enhanced CT-scan). An overall number of 18 (16.2%) SPDP-related sequelae was collected, but no significant differences were found between WT and KT, see Table 3. Among the 18 patients with long-term sequelae, six (30%) had multiple sequelae. The most common long term sequelae was splenomegaly with perigastric varices (n = 3, 15%); others were splenic infarction and varices (n = 1), splenic infarction and therapy with antiplatelets for thrombocytosis (n = 1), splenic infarction with perigastric varices and therapy with antiplatelets for thrombocytosis (n = 1). Most of the first sequelae occurred within the first 12 months (n = 13, 72.2%).

There was no difference in the incidence of perigastric varices between the WT and KT groups (12.1% vs 8.9%, p = 0.692). Of note, none of these patients reported clinical consequences of perigastric varices (such any form gastrointestinal bleeding, chronic anemia) or splenomegaly (such as left abdominal pain or discomfort, postprandial fullness, or signs of hypersplenism in terms of peripheral cytopenia). Kaplan–Meier analysis of the time-to-onset of a post-SPDP sequela did not reveal any statistically significant difference when comparing WT and KT (Fig. 1 A). When the analysis was stratified according to the type of surgical approach, the analysis showed a shorter time-to-onset in the open group (p = 0.032, log-rank test, Fig. 1 B). Considering the single sequela, none of them revealed a shorter time-to-onset or differences between groups.

Table 1
Baseline and perioperative characteristics.

Variable	Overall (n = 164)	WT (n = 55)	KT (n = 109)	p-value
Age (years), median(IQR), 95%CI_{median}	52 (24), 49–54	50 (27), 47–55	54 (23), 49–58	0.547
Female sex, n, %	124 (75.6)	40 (72.7)	84 (77.1)	0.567
ASA score, median, IQR	2 (1–3)	2 (0)	2 (1)	0.991
Tumor size (mm), median(IQR), 95%CI_{median}	24.5 (25), 20.5–27	30 (28), 20-35	23 (23), 20-25	0.209§
BMI, mean, SD	26.1 ± 4.4	26.2 ± 4.5	26.1 ± 4.8	1.0
Pathology, n, %				
Neuroendocrine tumor	53 (32.3)	17 (30.9)	36 (33)	0.391
Mucinous cystadenoma	23 (14)	11 (20)	12 (11)	
Serous cystadenoma	22 (13.4)	4 (3.7)	18 (16.5)	
IPMN	22 (13.4)	7 (12.7)	15 (13.8)	
SPT	12 (7.3)	3 (5.5)	9 (8.3)	
Chronic pancreatitis	12 (7.3)	4 (3.7)	8 (7.3)	
PDAC	1 (0.06)	–	1 (0.6)	
Other	12 (7.3)	3 (5.5)	9 (8.3)	
Unknown	10 (6.1)	6 (10.9)	4 (3.7)	
Minimally-invasive, n, %	95 (57.9)	22 (40)	73 (66.9%)	**0.001**
Laparoscopic	91 (95.7)	20 (36.3)	71 (65.1)	
Robot-assisted	4 (4.3)	2 (3.6)	2 (1.8)	
Estimated blood loss, median(IQR), 95%CI_{median}	186 (164), 155-200	200 (240), 192-300	160 (150), 145-200	**0.017**§
Operative time (min), median(IQR), 95%CI_{median}	195 (82), 185–210	181 (82), 165–212	195 (98), 185-214	0.107§
Length of stay (d), median(IQR), 95%CI_{median}	8 (5), 8–8	8 (4), 8–9	8 (5), 7–9	0.592§

ASA: American Society of Anesthesiologists; BMI: body mass index. IPMN. Intraductal papillary mucinous neoplasm; SPT: solid pseudopapillary tumor. PDAC: pancreatic adenocarcinoma; EBL: estimated blood loss. *Values in. Bold are statistically significant.
§ = Mann-Whitney *U* test.

Table 2
Postoperative outcomes after SPDP, comparing WT with KT and MI with open SPDP.

Variable	Overall (n = 164)	WT (n = 55)	KT (n = 109)	p-value	MI (n = 95)	Open (n = 69)	p-value
Any complication, n(%)	87 (53)	30 (54.5)	57 (52.3)	0.869	50 (52.6)	37 (53.6)	1
CDC ≥ 3, n(%)	20 (12.2)	7 (12.7)	13 (11.9)	1.0	11 (11.6)	9 (13)	0.812
CR-POPF, n(%)	64 (39)	23 (41.8)	41 (37.6)	0.615	40 (42.1)	24 (34.7)	0.418
PPH, n(%)	12 (7.3)	5 (9.1)	7 (6.4)	0.539	7 (7.4)	5 (7.2)	1.0
DGE, n(%)	7 (4.3)	5 (9.1)	2 (1.8)	**0.043**[a]	0 (0)	7 (10.1)	**0.002**[a]
Abdominal abscess, n(%)	21 (12.8)	5 (9.1)	16 (14.7)	0.458	8 (8.4)	13 (18.8)	**0.03**
Splenic infarct, n(%)	12 (7.3)	2 (3.6)	10 (9.2)	0.341[a]	3 (3.2)	9 (13)	**0.042**[a]
Splenectomy, n(%)	4 (2.4)	2 (3.6)	2 (1.8)	0.603[a]	1 (1.4)	3 (3.2)	0.639[a]
ICU admission, n(%)	5 (3)	1 (1.8)	4 (3.7)	0.665[a]	3 (3.2)	2 (2.9)	1.0[a]
Reintervention, n(%)	9 (5.5)	3 (5.5)	6 (5.5)	1.0[a]	5 (5.3)	4 (5.8)	1.0[a]
Readmission, n(%)	17 (10.4)	7 (12.4)	10 (9.2)	0.588[a]	11 (11.6)	6 (8.7)	0.812[a]
GI bleeding, n(%)	1 (0.6)	0 (0)	1 (0.9)	1.0[a]	1 (1.1)	0 (0)	1.0[a]

CDC: Clavien-Dindo classification; CR-POPF: clinically-relevant postoperative pancreatic fistula; PPH: post-pancreatectomy hemorrhage; ICU: intensive care unit. *Values in bold are statistically significant.
[a] Fisher's exact test.

Table 3
Long-term sequelae after SPDP.

Variable	Overall (n = 111)	WT (n = 33)	KT (n = 79)	p-value	MI (n = 64)	Open (n = 47)	p-value
Any sequela, n, (%)	18 (16.2)	5 (15.1)	13 (16.6)	0.768	8 (12.5)	10 (21.2)	**0.032**
Perigastric varices, n,(%)	11 (9)	4 (12.1)	7 (8.9)	0.735[a]	6 (9)	5 (10.6)	0.751[a]
Splenic infarction, n,(%)	6 (5.4)	1 (3)	5 (6.4)	0.666[a]	2 (3.1)	4 (8.5)	0.212[a]
Splenomegaly, n, (%)	5 (4.5)	2 (6)	3 (3.8)	0.642[a]	3 (4.6)	2 (4.2)	0.1[a]
Thrombocytosis w need for antiplatelets, n,(%)	3 (2.7)	0	3 (3.8)	0.551[a]	1 (1.5)	2 (4.2)	0.572[a]
ID-NODM, n(%)	9 (13.6), n = 66	2 (18), n = 11	7 (12.7), n = 55	0.713[a]	7 (12.7), n = 55	2 (18), n = 11	0.713[a]
Other[b], n(%)	1 (0.9)	0	1[b](1.2)	1.0[a]	1 (1.5)	0	1.0[a]

ID-NODM: insulin-dependent new onset diabetes mellitus.
*Values in old are statistically significant.
[a] Fisher's exact test.
[b] = post-trauatic splenic rupture.

Long-term outcomes: MI vs. open

MI-SPDP was associated with less SPDP-sequelae (12.5% vs. 21.2%, p = 0.032, Table 3). No differences in single sequelae were observed between the groups.

Discussion

This international retrospective study found comparable short- and long-term outcomes with the WT and KT techniques for SPDP. Postoperative complications only differed for DGE between both techniques. Follow-up revealed 16.2% long-term sequelae for WT and KT. MI SPDP was associated with less short-term complications (less DGE, less abdominal abscesses and less splenic infarction) and less long-term overall sequelae as compared to open SPDP.

Several meta-analyses of mostly retrospective studies concluded that KT should be preferred over WT, since it is associated with less splenogastric complications (in terms of perigastric varices and splenic infarctions, and splenectomy), or postoperative complications [7,13–17]. The present study found very similar differences in terms of postoperative complications between the two techniques, that demonstrated to be both safe and viable. It must be kept in mind that randomized controlled studies are lacking and thus surgeons adopt the technique they are most confident with.

As regards the development of long-term sequelae, previous studies reported perigastric varices as the most frequent, occurring in up to 27% of cases [24]; however even after a long-term follow-up this finding does not have any apparent clinical impact [24,25]. This study found a slightly lower rate of perigastric varices (9%) and no clinically relevant gastrointestinal bleeding (due to perigastric varices). This finding was previously highlighted by other studies, also in those with only WT [24,25].

We found less long-term sequelae after MI as compared to open SPDP (12.1% vs 21.2%, p = 0.032). A clear explanation for this finding is lacking and we can therefore only hypothesize. The benefits of MI SPDP were observed both in WT and in KT. It could be that the more meticulous dissection with MI surgery and the fact that the MI approach allows for sparing the left gastroepiploic circulation is beneficial but this is mere speculation.

When considering the postoperative complications, only DGE differed between the two groups, (WT 9.1% vs. KT. 1.8%, p = 0.043). Notably, as far as we know, our study is the only one that reports this complication among all the possible ones after SPDP so far. Again, we can only hypothesize that MI approach, most often used for KT, allows preservation of the gastric veins and minimization of gastroepiploic ligament opening in order to spare the left gastroepiploic circulation. On the contrary, some surgeons also advocate against KT, as this would be associated with longer operative time and more intraoperative blood loss. This study did find trends but no significant differences for operative time. Instead, we found significantly less blood loss with MI surgery and with the KT approach. In general, considering the nil mortality and the acceptable and comparable rates of postoperative complications we can only conclude that WT and KT are both safe options for SPDP.

With regards to the surgical approach, we found less DGE, less abdominal abscesses and less splenic infarction in the MI group. Furthermore, the MI approach was associated with less blood loss and shorter hospital stay, as was recently confirmed in the LEOPARD trial, the first randomized trial on MI distal pancreatectomy [18]. Considering the trend towards a more diffuse use of MI pancreatic surgery [26], it is likely that in the near future the vast majority of SPDP procedures will be performed using a MI approach.

This study has several limitations that must be taken into

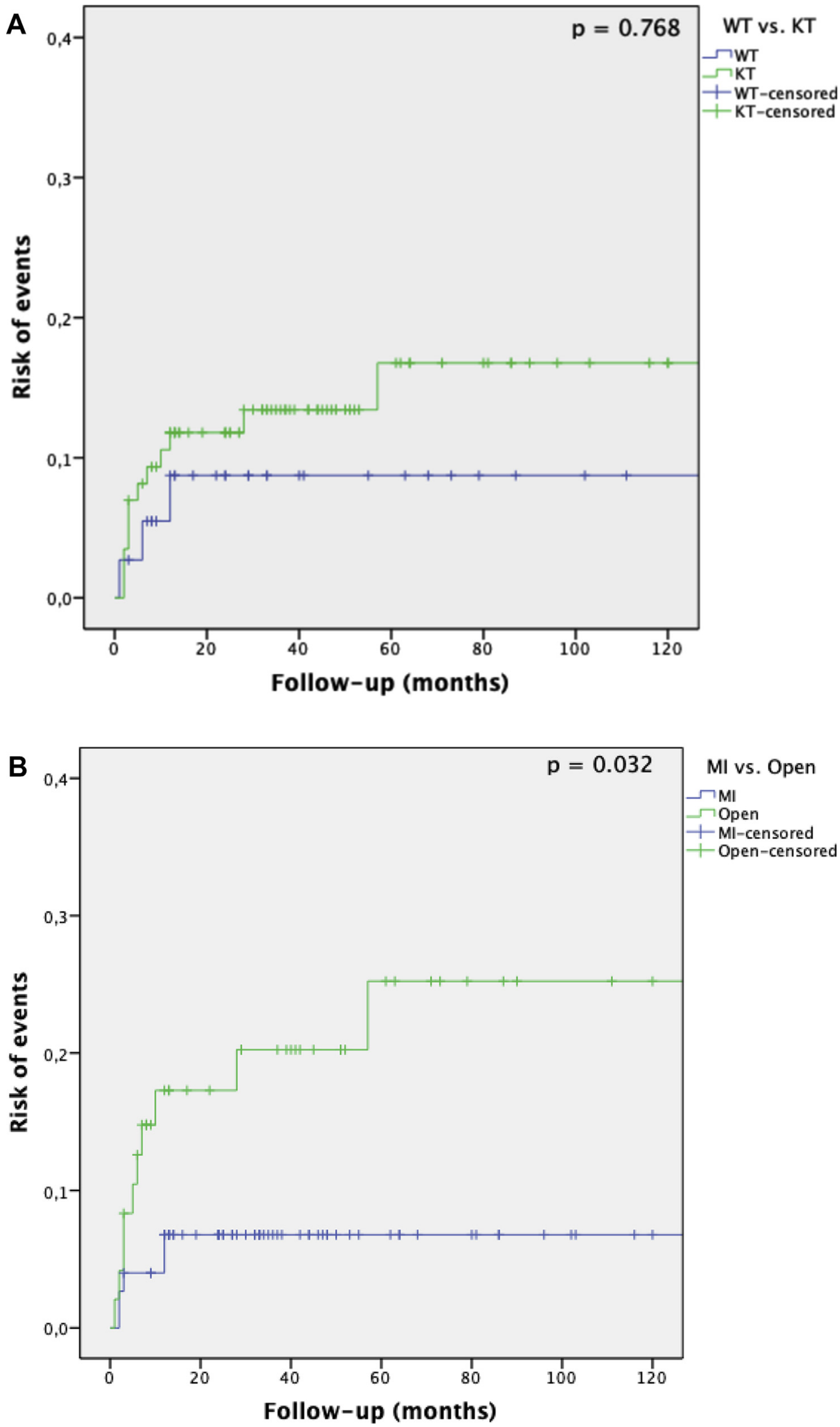

Fig. 1. Time-to-event analysis of long-term sequelae of SPDP. A) WT vs. KT; B) MI SPDP vs. open SPDP.

account. First, we did not manage to assess chronic signs of gastrointestinal bleeding (e.g. microcytic anemia or positive fecal occult blood test) or platelet disorders due to splenic dysfunction. Second, we could not collect data on the exact site of the original disease (such as how far from the spleen) and how this factor might have played a role in the surgical plan. Third, and more importantly, the retrospective nature did not allow us to collect information on the surgery planned in order to perform an intention-to-treat analysis (either to understand the reasons for choosing WT or KT, or to understand those cases that were planned as SPDP but that in the end they turned out to be distal pancreatectomy with splenectomy). For the same reason, we cannot reliably report a conversion rate for those cases performed with an MI approach and completed with an open one. It is known, however that this conversion rate in trained hands is very low. Nevertheless, this bias, together with the previous one, makes that we cannot exclude the possibility that preoperative patient features and surgical planning, and intraoperative surgical choices influenced either short-term complications and long-term sequelae.

The strengths of our project are the sample size, the international collaboration involving three high volume pancreatic centers and the additionally obtained long-term follow-up. Furthermore, no study has ever compared WT and KT with regard to the surgical technique (MI vs. open SPDP) so far. Thus, our findings as regards the possible benefits of MI-SPDP may be taken into account from now on and may drive guidelines or future prospective trials.

Conclusions

In our experience, WT and KT were associated with similar short- and long-term outcomes. KT was only associated with a lower rate of DGE compared to WT. The MI approach was associated with less long-term sequelae as compared to open SPDP. This study prudently suggests that an MI approach should be preferred for SPDP in benign or low-malignant pancreatic diseases of the body and tail of the pancreas. If a KT is not feasible, then a WT should be attempted, rather than performing a splenectomy. In general, surgeons should master both techniques in order to perform a splenectomy only when really necessary.

Support

No funding support.

Informed consent statement

Not applicable to this study.

Conflict-of-interest statement

None of the authors have received fees for serving as a speaker or are consultant/advisory board member for any organizations. None of the authors have received research funding from any organizations. None of the authors are employees of any organizations. None of the authors own stocks and/or share in any organizations. None of the authors own patents.

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