BJA

British Journal of Anaesthesia, 125 (2): 141–148 (2020)

doi: 10.1016/j.bja.2020.03.034
Advance Access Publication Date: 28 May 2020
Clinical Practice

Association between intraoperative intravenous lidocaine infusion and survival in patients undergoing pancreatectomy for pancreatic cancer: a retrospective study

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Abstract

Background: Intravenous lidocaine has been shown to reduce opioid consumption and is associated with favourable outcomes after surgery. In this study, we explored whether intraoperative lidocaine reduces intraoperative opioid use and length of stay (LOS) and improves long-term survival after pancreatic cancer surgery.

Methods: This retrospective study included 2239 patients who underwent pancreatectomy from January 2014 to December 2017. The patients were divided into non-lidocaine and lidocaine (bolus injection of 1.5 mg kg^{-1} at the induction of anaesthesia followed by a continuous infusion of 2 mg kg^{-1} h^{-1} intraoperatively) groups. The overall use of postoperative rescue analgesia and LOS were recorded. Propensity score matching was used to minimise bias, and disease-free survival and overall survival were compared between the two groups.

Results: After propensity score matching, patient characteristics were not significantly different between groups. Intraoperative sufentanil consumption and use of postoperative rescue analgesia in the lidocaine group were significantly lower than those in the non-lidocaine group. The LOS was similar between groups. There was no significant difference in disease-free survival between groups (hazard ratio [HR]=0.913; 95% confidence interval [CI], 0.821–1.612; P=0.316). The overall survival rates at 1 and 3 yr were significantly higher in the lidocaine group than in the non-lidocaine group (68.0% *vs* 62.6%, P<0.001; 34.1% *vs* 27.2%, P=0.011). The multivariable analysis indicated that intraoperative lidocaine infusion was associated with a prolonged overall survival (HR=0.616; 95% CI, 0.290–0.783; P=0.013).

Conclusion: Intraoperative intravenous lidocaine infusion was associated with improved overall survival in patients undergoing pancreatectomy.

Keywords: disease-free survival; lidocaine; mortality; overall survival; pancreatic cancer; postoperative recovery

Received: 26 November 2019; **Accepted:** 17 March 2020

Editor's key points

- This retrospective observational study evaluated whether intraoperative lidocaine infusion is associated with improved outcomes after pancreatic cancer surgery.
- Overall, 3- to 5-yr outcomes were poor, with a modest improvement in early (1–3 yr) overall survival in patients who received lidocaine, but no significant improvement in disease-free survival.
- It is unlikely that intravenous lidocaine substantially, if at all, improves outcomes after pancreatic surgery.
- This study is hypothesis-generating and warrants further research rather than clinical translation.

Pancreatic cancer is an aggressive malignancy and is the fourth leading cause of cancer-related death worldwide.[1] Although substantial progress has been made in the diagnosis and treatment of this disease, the 5-yr survival rate remains low at approximately 6%.[2] This concerning statistic is evidence that there is an urgent need to discover and develop strategies that can extend the survival of patients with pancreatic cancer.

Experimental studies have shown that anaesthetics might influence tumour progression; however, the clinical evidence is conflicting.[3,4] Lidocaine is an amide local anaesthetic commonly used during cancer surgery. Lidocaine, both *in vitro* and *in vivo*, can act directly and indirectly on pancreatic cancer cells and the tumour microenvironment.[5,6] At the tumour level, lidocaine can induce apoptosis in cancer cells by inhibiting Src phosphorylation and reducing the expression of adhesion molecules.[7,8] In the tumour microenvironment, lidocaine can enhance the activity of immune cells such as natural killer cells, which are responsible for directly attacking cancer cells.[9,10] Furthermore, lidocaine can reduce intraoperative opioid consumption.[11] A recent retrospective study demonstrates that opioid use has been associated with pancreatic cancer progression.[12] Hence, lidocaine appears to have predominantly anticancer effects.

Intravenous lidocaine infusions are also used during surgery as they improve overall postoperative outcomes in patients undergoing colorectal cancer surgery.[13] In major abdominal surgery, intravenous infusion of lidocaine significantly reduces postoperative pain, has opioid-sparing effects, promotes gastrointestinal function recovery, and shortens the postoperative hospital stay.[13–15]

However, it is unclear whether intravenous lidocaine infusion during pancreatic cancer surgery is associated with any improvements in surgical recovery and long-term oncologic outcomes. Therefore, we conducted a retrospective study to evaluate the association between intravenous infusions of lidocaine during pancreatic cancer surgery and long-term patient survival outcomes, specifically disease-free (DFS) and overall survival (OS). In this study, we hypothesised that use of lidocaine is an independent predictor of improved survival outcomes in patients undergoing pancreatectomy. We also studied the associations between the intraoperative use of lidocaine and intraoperative sufentanil consumption, postoperative analgesia, and hospital length of stay (LOS).

Methods

This study was retrospective and approved by the Ethics Committee of Fudan University Shanghai Cancer Centre (FUSCC), China (protocol# 1907204-7). Patients undergoing scheduled pancreatic cancer surgery from January 2014 to December 2017 at the FUSCC were included. The inclusion criteria were as follows: (1) aged 18 yr or older; (2) underwent R0 resection (circumferential resection margin of 1 mm) for pancreatic ductal adenocarcinoma (PDAC) identified by pathology; (3) did not have any history of another malignant tumour; (4) did not have any history of antitumor treatments before surgery; (5) did not die within 30 days of surgery from postoperative complications; (6) received combined general–epidural anaesthesia; and (7) had complete clinicopathological and follow-up data. Patients were excluded if they underwent emergency surgery or were lost to follow-up.

Endpoints

The primary endpoints of this study were DFS and OS. OS was defined as the period from the patient's date of surgery to the time of death or last follow-up. DFS was defined as the interval between the date of surgery and the date of tumour recurrence or December 31, 2018. Follow-up was continued until December 31, 2018 or until the patient died. The secondary endpoints included intraoperative sufentanil consumption, overall use of postoperative rescue analgesia, and length of postoperative hospital stay.

Exposure variable

We were interested in the effect of lidocaine on short- and long-term outcomes after pancreatic surgery. Patients in the lidocaine group received an initial bolus of lidocaine (1.5 mg kg^{-1}) at the induction of general anaesthesia, followed by a continuous infusion of 2 mg kg^{-1} h^{-1} intraoperatively that was stopped at the end of surgery. In the non-lidocaine group, the patients did not receive intravenous local anaesthetics.

Anaesthesia care

Upon entering the operating room, all patients were monitored according to the American Society of Anesthesiologists (ASA) monitoring standards. In all patients, general anaesthesia was induced with sufentanil (0.3–0.5 μg kg^{-1}), propofol (target-controlled infusion, effect-site concentration: 3.0–4.0 μg ml^{-1}), and rocuronium (0.6 mg kg^{-1}). The patients were then tracheally intubated, and general anaesthesia was maintained with 2.0–3.0% sevoflurane in an oxygen/air mixture. Repeated bolus injections of sufentanil and rocuronium were given as necessary throughout the operation. All patients in the study received epidural analgesia with an infusion of 0.375–0.5% ropivacaine via an epidural catheter placed at the mid-thoracic level (T7–T9). At the end of the operation, all patients received a patient-controlled epidural analgesia (PCEA) pump (0.1% ropivacaine and 0.5 μg ml^{-1} sufentanil, background: 3 ml h^{-1}, bolus: 4 ml, lockout time: 15 min) for 48 h. A dose of 50 mg flurbiprofen was used for postoperative rescue analgesia per times.

Statistical analysis

The data were retrospectively collected from the database of the FUSCC clinical information system. The medical information, including the baseline patient characteristics, primary diagnosis, use of adjuvant treatment, TNM stage, medical history including Charlson comorbidity index, operative details (procedure type and estimated blood loss), anaesthesia methods, and pathology results were reviewed and recorded for each patient. Intraoperative sufentanil consumption, overall use of postoperative rescue analgesia with flurbiprofen, and length of postoperative hospital stay were recorded. We performed 1–5 yr of follow-up (every 3 months for the 1st and 2nd years and every 6 months for the 3rd year) by reviewing medical records and initiating telephone contact.

Patient characteristics, disease status, intraoperative variables, and outcomes were summarised through descriptive statistics. In addition, *t*-tests or Mann–Whitney U tests were used to compare continuous variables between patient groups. Fisher's exact text or χ^2 test was used to evaluate the associations between categorical variables. Categorical data are expressed as *n* (%) and analysed with the χ^2 test; continuous data are expressed as the mean (standard deviation, SD), and two independent samples were analysed with the *t*-test. The Kaplan–Meier method was used to calculate OS and DFS. Cox proportional hazards regression models were used to compare risk factors between the different groups by using univariate models. Variables that were significant in the univariate analysis were entered into a multivariate model using the forward conditional method, which was used to fit the multivariate model.

We performed propensity score matching analysis to reduce selection bias by building a matched group of patients to compare OS and DFS between patients who did and did not receive lidocaine infusions. Eight variables were entered in our propensity model: age, sex, ASA physical status, Charlson comorbidity index, tumour differentiation, TNM stage, surgery type, and administration of adjuvant treatment. The patients were matched using a 5-to-1 digit greedy match algorithm. Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA), and a *P*-value <0.05 was considered statistically significant.

Results

A total of 2239 patients who underwent pancreatectomy for pancreatic cancer were enrolled in this study. After the inclusion criteria were applied, 1191 patients remained in the non-lidocaine group, and 915 patients remained in the lidocaine infusion group. After propensity score matching, 915 patients remained in the non-lidocaine infusion group, and 915 remained in the lidocaine infusion group (Fig. 1). Patient characteristics, including age, sex, American Society of Anesthesiologists (ASA) physical status, operative variables, and TNM staging, were similar between the groups (Table 1).

Primary endpoint

In this study, the median follow-up time for all patients was 16.2 months (95% CI, 13.7, 16.6). The Kaplan–Meier survival curves for the lidocaine infusion and non-lidocaine infusion

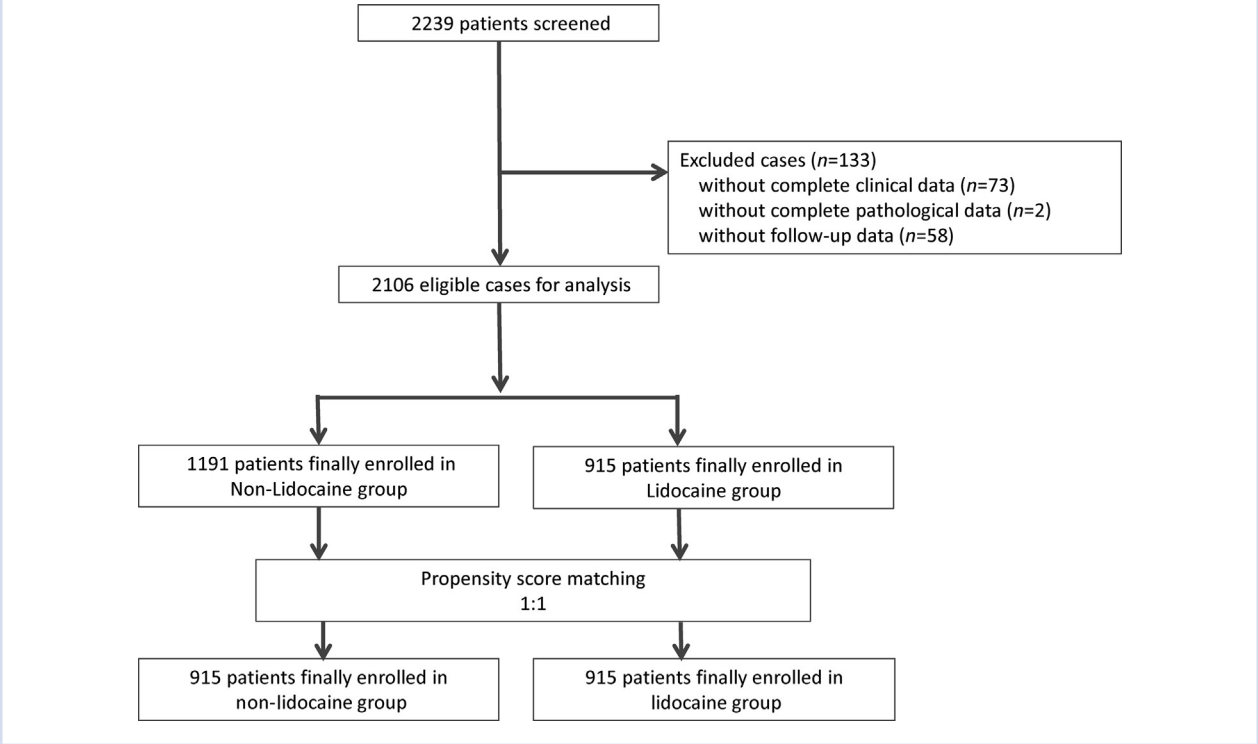

Fig 1. Flow diagram detailing the selection process for patients included in this retrospective analysis. A total of 133 patients were excluded because of incomplete clinical data, pathological data or lack of follow-up data.

Table 1 Patient and treatment characteristics for both groups. IQR, inter-quartile range; CCI, Charlson comorbidity index; AJCC 8th TNM stage, American Joint Committee on Cancer, 8th edition; OS, overall survival; DFS, disease-free survival.

Variable	Original cohort		P	Matched cohort		P	Standard difference
	Non-lidocaine group (*n*=1191)	Lidocaine group (*n*=915)		Non-lidocaine group (*n*=915)	Lidocaine group (*n*=915)		
Age (median–IQR, year)	58 (46–69)	56 (46–66)	<0.001	56 (46–67)	56 (46–66)	0.711	5.82
Sex (*n*, %)			0.421			0.768	3.25
Female	394 (33.1%)	318 (34.7%)		312 (34.1%)	318 (34.7%)		–
Male	797 (66.9%)	597 (65.3%)		603 (65.9%)	597 (65.3%)		–
BMI kg m^{-2}, (median–IQR)	22.5 (20.5–25.3)	23.5 (20.7–25.6)	0.425	22.3 (20.3–23.9)	23.0 (20.7–25.3)	0.526	–
ASA physical status (*n*, %)			0.008			0.792	2.13
1	197 (16.6%)	138 (15.1%)		133 (14.6%)	138 (15.1%)		–
2	921 (77.3%)	746 (81.6%)		746 (81.6%)	746 (81.6%)		–
3	73 (6.1%)	31 (3.3%)		36 (3.8%)	31 (3.3%)		–
Patients enrolled			0.873			0.998	
2014	294 (24.7%)	230 (25.1%)		232 (25.4%)	230 (25.1%)		
2015	302 (25.3%)	219 (23.9%)		217 (23.7%)	219 (23.9%)		
2016	298 (25.1%)	228 (26.0%)		226 (24.7%)	228 (26.0%)		
2017	297 (24.9%)	238 (26.0%)		240 (26.2%)	238 (26.0%)		
CCI (*n*, %)			0.554			0.970	–
0	743 (62.4%)	589 (64.4%)		591 (64.6%)	589 (64.4%)		–
1	326 (27.4%)	243 (26.6%)		239 (26.2%)	243 (26.6%)		3.12
≥2	122 (10.2%)	83 (9%)		85 (9.2%)	83 (9%)		
Tumour differentiation (*n*, %)			0.224			0.775	2.36
Well–moderate	448 (37.6%)	368 (40.3%)		362 (39.6%)	368 (40.3%)		–
Poor	743 (62.4%)	547 (59.7%)		553 (58.5%)	547 (59.7%)		–
Nerve invasion (*n*, %)			0.331			0.491	–
Yes	1054 (88.5%)	797 (87.1%)		794 (86.8%)	797 (87.1%)		–
No	137 (11.5%)	118 (12.9%)		122 (13.2%)	118 (12.9%)		–
T stage (*n*, %)			0.355			0.963	–
1	301 (25.3%)	225 (24.6%)		222 (24.3%)	225 (24.6%)		–
2	806 (67.7%)	610 (66.7%)		610 (66.7%)	610 (66.7%)		–
3	84 (7%)	80 (8.7%)		83 (9%)	80 (8.7%)		–
N stage (*n*, %)			0.813			0.968	–
0	600 (53.0%)	471 (51.5%)		466 (51.0%)	471 (51.5%)		–
1	434 (36.5%)	331 (36.2%)		336 (36.8%)	331 (36.2%)		–
2	157 (10.5%)	113 (12.3%)		113 (12.2%)	113 (12.3%)		–
AJCC 8th edition TNM stage (*n*, %)			0.822			0.838	3.62
I	600 (50.4%)	452 (49.4%)		452 (49.4%)	452 (49.4%)		–
II	432 (36.3%)	344 (37.6%)		336 (36.8%)	344 (37.6%)		–
III	159 (13.3%)	119 (13%)		127 (13.8%)	119 (13%)		–
Tumour size (*n*, %)			0.173			0.783	–
≤5 cm	883 (74.2%)	702 (76.7%)		697 (76.2%)	702 (76.7%)		–
>5 cm	308 (25.8%)	213 (23.3%)		218 (23.8%)	213 (23.3%)		–
Surgery type (*n*, %)			0.859			0.475	4.52
Pancreaticoduodenectomy	701 (58.9%)	529 (57.8%)		524 (57.3%)	529 (57.8%)		–
Distal pancreatectomy	469 (39.4%)	368 (40.2%)		365 (39.9%)	368 (40.2%)		–
Total pancreatectomy	21 (1.7%)	18 (2%)		26 (2.8%)	18 (2%)		–
Tumour location (*n*, %)			0.840			0.961	–
Head of pancreas	759 (63.7%)	587 (64.2%)		588 (64.2%)	587 (64.2%)		
Tail of pancreas	432 (36.3%)	328 (35.8%)		327 (35.8%)	328 (35.8%)		
Estimated blood loss (*n*, %)			0.217			0.822	–
≤400 ml	898 (75.4%)	711 (77.7%)		715 (78.2%)	711 (77.7%)		–
>400 ml	293 (24.6%)	204 (22.3%)		200 (21.8%)	204 (22.3%)		–
Blood transfusion			0.766			0.779	–
No	1105 (92.8%)	852 (93.1%)		855 (93.4%)	852 (93.1%)		
Yes	86 (7.2%)	63 (6.9%)		60 (6.6%)	63 (6.9%)		
Adjuvant treatment (*n*, %)			<0.001			0.904	2.64
No	838 (70.4%)	747 (81.6%)		745 (81.4%)	747 (81.6%)		–
Yes	353 (29.6%)	168 (19.4%)		170 (18.6%)	168 (19.4%)		–
Adjuvant treatment across year (*n*, %)			0.997			0.957	
2014	95 (27.0%)	46 (27.3%)		44 (26.0%)	46 (27.3%)		
2015	86 (24.4%)	41 (24.7%)		45 (26.4%)	41 (24.7%)		
2016	83 (23.5%)	38 (23.1%)		40 (23.5%)	38 (23.1%)		
2017	89 (25.1%)	43 (24.9%)		41 (24.1%)	43 (24.9%)		

groups are displayed in Figure 2. The DFS rates at 1 and 3 yr after surgery were not different between patients in the non-lidocaine group and those in the lidocaine infusion group (1 yr DFS: 56.2%, [514/915] *vs* 57.5% [526/915], *P*=0.888; 3 yr DFS: 12.5% [114/915] *vs* 15.2% [139/915], *P*=0.390; Fig. 2a). The univariate Cox regression analysis showed that tumour differentiation (*P*=0.015), nerve invasion (*P*=0.022), T stage (*P*=0.010), N stage (*P*=0.032), TNM stage (*P*=0.003), and adjuvant treatment (*P*=0.021) were associated with DFS in the original cohort (Table 2). In the multivariable Cox proportional hazards model before propensity score matching, the following variables were significantly associated with an unfavourable DFS: poor tumour differentiation (HR=1.113; 95% CI, 1.021, 1.912; *P*=0.006), nerve invasion (HR=1.312; 95% CI, 1.106, 1.463; *P*=0.017), and no adjuvant treatment (HR=1.455; 95% CI, 1.321, 1.702; *P*=0.012). The association between non-lidocaine infusion and DFS was not statistically significant in the model (HR=0.943; 95% CI, 0.621, 1.000; *P*=0.176; Table 3). After propensity score matching, the association between non-lidocaine infusion and DFS was still not statistically significant (HR=0.913; 95% CI, 0.821, 1.612; *P*=0.316). The following variables remained statistically significant in the model: tumour differentiation (HR=1.114; 95% CI, 1.106, 1.519; *P*=0.018), nerve invasion (HR=1.135; 95% CI, 1.008, 1.316; *P*=0.023), and lack of adjuvant treatment (HR=1.155; 95% CI, 1.034, 1.235; *P*=0.024; Table 3).

The Kaplan–Meier curves for OS suggest that patients who were treated with lidocaine had a significant improvement in survival. The OS rates at 1 and 3 yr after surgery were significantly higher for the patients in the lidocaine infusion group than for those in the non-lidocaine infusion group (1 yr OS: 68.0% [622/915] *vs* 62.6% [573/915], *P*<0.001; 3 yr OS: 34.1% [312/915] *vs* 27.2% [248/915], *P*=0.011, respectively; Fig. 2b). The univariate Cox regression analysis showed that tumour differentiation, nerve invasion, T stage, N stage, TNM stage, and adjuvant treatment were associated with OS in the original cohort (Table 2). The multivariable analysis before propensity score matching showed that the following variables were significantly associated with an unfavourable OS: poor tumour differentiation (HR=1.204; 95% CI, 1.100, 1.409; *P*=0.018), nerve invasion (HR=1.235; 95% CI, 1.108, 1.416; *P*=0.012), and no adjuvant treatment (HR=1.055; 95% CI, 1.034, 1.386; *P*=0.006) (Table 3). Intravenous infusions of lidocaine were associated with a prolonged OS (HR=0.762; 95% CI, 0.427, 0.902; *P*<0.001). After propensity score matching, the association between lidocaine infusion and OS remained statistically significant (HR=0.616; 95% CI, 0.290, 0.783; *P*=0.013). The following variables were also statistically significant: tumour differentiation (HR=1.104; 95% CI, 1.002, 1.322; *P*=0.014), nerve invasion (HR=1.112; 95% CI, 1.106, 1.316; *P*=0.032), and adjuvant treatment (HR=1.022; 95% CI, 1.004, 1.186; *P*=0.016; Table 3).

Secondary outcomes

The mean (SD) intraoperative sufentanil consumption was significantly lower in the lidocaine group (46.9 [8.6] μg) than in the non-lidocaine group (55.1 [9.5] μg) (*P*<0.001; Fig. 3a). The average (SD) use of postoperative rescue analgesia after surgery was significantly lower in the lidocaine infusion group than in the non-lidocaine group (3.2 [1.1] *vs* 4.3 [1.3], *P*<0.001; Fig. 3b). In terms of the length of hospital stay, the median duration (inter-quartile range) in the non-lidocaine group was 18.3 (16.0, 21.7) days, whereas in the lidocaine group, the mean LOS was 17.9 days (15.7, 21.1) (*P*=0.154; Fig. 3c).

Discussion

To the best of our knowledge, this is the first study to evaluate the association between the use of lidocaine infusion during pancreatectomy for pancreatic cancer and DFS and OS in a large cohort of patients. Briefly, we observed that patients who received an intraoperative infusion of lidocaine had a longer OS, but not DFS, than those who did not receive the local anaesthetic. Our study also showed the following: (1) an infusion of lidocaine was associated with a significant opioid-sparing effect although patients in both groups received thoracic epidural analgesia, and (2) an infusion of lidocaine reduced the requirement for rescue analgesia.

Although the discrepancies in OS and DFS might be difficult to reconcile, it is important to consider that in pancreatic cancer, DFS cannot be used as an appropriate surrogate of OS, as shown by a low correlation (R^2 = 0.44–0.65) in RCTs.[16] Furthermore, when analysing different types of survival in patients with pancreatic cancer, there are competing risks that might influence both types of survival differently, such as

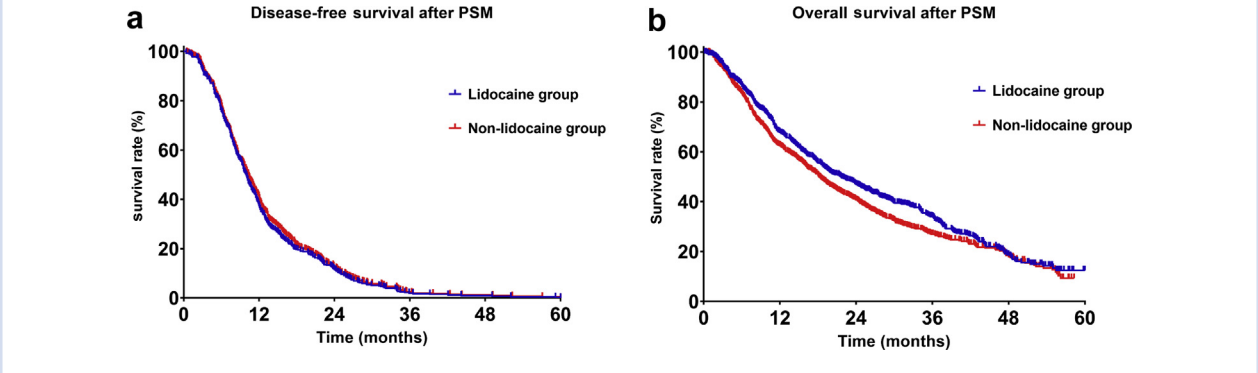

Fig 2. (a) Disease-free survival curves from the date of surgery according to the use of intraoperative intravenous lidocaine infusion. (b) Overall survival curves from the date of surgery according to the use of intraoperative intravenous lidocaine infusion. DFS; disease-free survival, OS; overall survival; PSM, propensity score matching.

Table 2 Univariate analysis of OS and DFS. IQR, inter-quartile range; CCI, Charlson comorbidity index; AJCC 8th TNM stage, American Joint Committee on Cancer, 8th edition; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Variables	OS		DFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.002 (0.985, 1.112)	0.921	1.032 (0.883, 1.112)	0.654
Sex (male *vs* female)	1.045 (0.726, 1.526)	0.795	1.054 (0.945, 1.112)	0.675
BMI	1.003 (0.943, 1.065)	0.884	1.132 (0.834, 1.392)	0.764
ASA score (1 *vs* 2. *vs* 3)	1.053 (0.700, 1.463)	0.805	1.089 (0.985, 1.162)	0.072
CCI (0 *vs* 1 *vs* ≥2)	0.848 (0.642, 1.108)	0.265	0.895 (0.385, 1.012)	0.126
Tumour differentiation (Poor)	1.909 (1.315, 2.765)	0.001	2.002 (1.484, 2.153)	0.015
Nerve invasion (Yes)	1.162 (1.048, 1.758)	0.025	1.092 (1.015, 1.112)	0.022
T stage (1 *vs* 2 *vs* 3)	1.458 (1.041, 2.048)	0.028	1.543 (1.285, 1.934)	0.010
N stage (0 *vs* 1 *vs* 2)	1.294 (1.006, 1.657)	0.042	1.675 (1.185, 1.912)	0.032
AJCC TNM stage (I *vs* II *vs* III)	1.335 (1.037, 1.718)	0.025	1.543 (1.123, 1.712)	0.003
Adjuvant treatment (Yes *vs* No)	0.415 (0.298, 0.589)	<0.001	0.564 (0.385, 0.712)	0.021
Estimated blood loss	1.000 (0.999, 1.001)	0.712	1.012 (0.985, 1.312)	0.545
Lidocaine infusion (Yes *vs* No)	0.486 (0.131, 0.635)	0.035	0.502 (0.387, 1.712)	0.071

Table 3 Multivariable Cox proportional of overall survival (OS) and disease-free survival (DFS). HR, hazard ratio, CI, confidence interval.

Variables	OS (before matching)		OS (after matching)		DFS (before matching)		DFS (after matching)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Lidocaine infusion (Yes *vs* No)	0.762 (0.427, 0.902)	<0.001	0.616 (0.290, 0.783)	0.013	0.943 (0.621, 1.000)	0.176	0.913 (0.821, 1.612)	0.316
Tumour differentiation (Poor)	1.204 (1.100, 1.409)	0.018	1.104 (1.002, 1.322)	0.014	1.113 (1.021, 1.912)	0.006	1.114 (1.106, 1.519)	0.018
Nerve invasion (Yes *vs* No)	1.235 (1.108, 1.416)	0.012	1.112 (1.106, 1.316)	0.032	1.312 (1.106, 1.463)	0.017	1.135 (1.008, 1.316)	0.023
Adjuvant treatment (No *vs* Yes)	1.055 (1.034, 1.386)	0.006	1.022 (1.004, 1.186)	0.016	1.455 (1.321, 1.702)	0.012	1.155 (1.034, 1.235)	0.024

age.[17] Thus, we believe that a significant improvement in OS should be considered a clinically relevant finding in our study.

The literature indicates that systemic lidocaine can be used to reduce perioperative analgesic consumption.[18] Opioids have been associated with negative oncological outcomes in patients with advanced pancreatic cancers, and it has been speculated that opioids could promote tumour growth.[12,19] However, whether the reduction in perioperative opioid consumption in patients receiving lidocaine explains the observed improvement in OS in our study remains unknown. Alternatively, it has been suggested that lidocaine could improve oncological outcomes by improving the activity of natural killer cells or having a direct apoptotic effect in cancer cells.[5,9,10] However, these effects of lidocaine were shown *in vitro*; therefore, the translation of these effects into clinical outcomes also remains unclear.

The infusion of lidocaine during and after surgery has been recommended as a means to improve short-term outcomes in patients undergoing abdominal surgery. However, the impact of lidocaine infusion on immediate postoperative outcomes after pancreatic surgery has unfortunately not been fully studied. Soliz and colleagues[20] reported that the use of total intravenous anaesthesia, in which lidocaine was one of the adjuvant anaesthetics, was associated with a reduced rate of postoperative complications. However, similar to our findings, that study also found that the LOS did not improve with total intravenous anaesthesia compared with volatile-opioid-based general anaesthesia. Therefore, it is unclear whether the addition of systemic lidocaine to the perioperative period of pancreatic cancer surgery enhances postoperative recovery.

Our study has several limitations. First, the retrospective design of our work is associated with bias and confounding owing to unknown and unmeasured variables that might have influenced the primary endpoints. Second, we restricted the analysis to a single large cancer centre. Third, we did not include surgeons in the analysis as a variable; therefore, it can be speculated that differences in survival could be confounded by the surgical outcomes of each surgeon. However, it is worth noting that in our centre, the administration of lidocaine is not based on surgeon preference. Fourth, we did not take into consideration possible time- and dose-dependent effects of lidocaine. It is possible to theorise that longer and higher concentrations of lidocaine might have stronger anticancer effects than shorter infusions or low levels of the local anaesthetic. Finally, we did not include in our analysis the inflammatory scores, severity of postoperative complications, or time needed to return to intended oncologic treatment. Although these are important variables and outcomes, at the

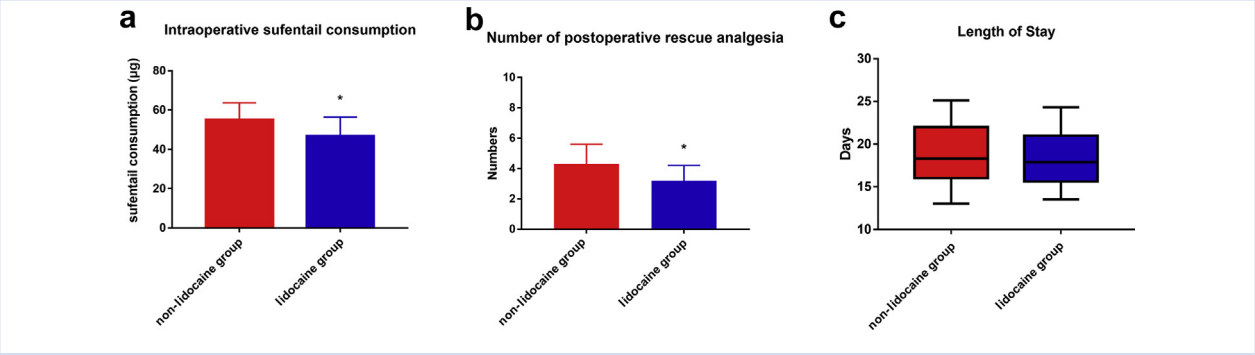

Fig 3. (a) Intraoperative sufentanil consumption between groups. (b) Overall use of postoperative rescue analgesia between groups. (c) Length of postoperative hospital stay between groups. * $P<0.001$.

time of the study, our database did not include reliable data on these factors, which may add significant confounding to the analysis.

In conclusion, an intraoperative intravenous lidocaine infusion during pancreatic cancer surgery is associated with a reduction in intraoperative sufentanil consumption and a prolonged overall survival. Although these results may be promising, it is necessary to test our hypothesis with a rigorous RCT.

Authors' contributions

Study design: HZ, JPC, WKC, CHM
Coordination: XQZ, MMZ, ZRS
Data acquisition: HZ, WKC, XQZ
Data interpretation: LY, ZRS
Primary drafting: HZ, WKC, JPC
Drafting: JPC, HZ, WKC, CHM
Final approval of the manuscript: all authors

Declaration of interests

The authors declare that they have no conflicts of interest.

Funding

National Natural Science Foundation of China (No. 81873948, No. 81871590, No. 81871591), the National Key Research and Development Program of China (No: 2018YFC2001904), Shanghai Shenkang Hospital Development Centre Clinical Science and Technology Innovation project (No. SHDC12018105), the Key Technology and Development Program of Shanghai (No. 17411963400).

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Handling editor: Michael Avidan