

Perioperative Glucocorticoids are Associated with Improved Recurrence-Free Survival After Pancreatic Cancer Surgery: A Retrospective Cohort Study with Propensity Score-Matching

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Purpose: Perioperative anesthetic management may affect long-term outcome after cancer surgery. This study investigated the effect of perioperative glucocorticoids on long-term survival in patients after radical resection for pancreatic cancer.

Methods: In this retrospective cohort study with propensity score-matching, patients who underwent radical resection for pancreatic cancer from January 2005 to December 2016 were recruited. Baseline and perioperative data including use of glucocorticoids for prevention of postoperative nausea and vomiting were collected. Patients were followed up by qualified personnel for cancer recurrence and survival. The primary outcome was the recurrence-free survival. Outcomes were compared before and after propensity matching. The association between perioperative glucocorticoid use and recurrence-free survival was analyzed with multivariable regression models.

Results: A total of 215 patients were included in the study; of these, 112 received perioperative glucocorticoids and 103 did not. Patients were followed up for a median of 74.0 months (95% confidence interval [CI] 68.3–79.7). After propensity score-matching, 64 patients remained in each group. The recurrence-free survivals were significantly longer in patients with glucocorticoids than in those without (full cohort: median 12.0 months [95% CI 6.0–28.0] vs 6.9 months [4.2–17.0], $P<0.001$; matched cohort: median 12.0 months [95% CI 5.8–26.3] vs 8.3 months [4.3–18.2], $P=0.015$). After correction for confounding factors, perioperative glucocorticoids were significantly associated with prolonged recurrence-free survivals (full cohort: HR 0.66, 95% CI 0.48–0.92, $P=0.015$; matched cohort: HR 0.54, 95% CI 0.35–0.84, $P=0.007$).

Conclusion: Perioperative use of low-dose glucocorticoids is associated with improved recurrence-free survival in patients following radical surgery for pancreatic cancer.

Keywords: pancreatic cancer, surgery, perioperative management, glucocorticoids, survival

Introduction

Pancreatic cancer is a malignant tumor with high mortality. According to the latest Global Cancer Statistics, 459,000 new cases of pancreatic cancer were diagnosed and 432,000 cases died in 2018, ranking as the seventh leading cause of cancer death worldwide.¹ According to the Chinese data, 90,100 new cases of pancreatic cancer were diagnosed and 79,400 cases died in 2015.² Currently, surgical resection accompanied by systemic adjuvant chemotherapy is the only possible treatment for

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patients to achieve prolonged survival.³ However, recent evidence showed that the clinical outcome of pancreatic cancer patients remains poor even after radical resection and modern adjuvant chemotherapy, with a median overall survival of 28–54 months.⁴ Recurrence and metastasis are the main reasons leading to short survival after pancreatic cancer surgery. This is because that the pancreatic cancer cells invade the lymphatic system and form micro-metastases at the very early stage, which make radical resection incomplete.⁴ Furthermore, surgery-related inflammation may also promote tumor growth and metastasis.⁵

Anesthetic management may affect the prognosis of cancer patients by regulating perioperative immunity and inflammation. For example, epidural block, dexmedetomidine, and non-steroidal anti-inflammatory drugs can blunt surgery-related stress response^{6,7} and, thus, may provide benefits for long-term outcome of some cancer patients.^{8–10} Low-dose glucocorticoids (dexamethasone or methylprednisolone) are frequently used to prevent postoperative nausea and vomiting;¹¹ in addition, they have transient effects on immune function and inflammatory response.¹² In animal studies of pancreatic cancer, inflammation increases the dissemination of cancer cells whereas dexamethasone abolishes this phenomenon.¹³ In two retrospective studies, perioperative low-dose dexamethasone was found to be associated with improved survival after pancreatic cancer surgery.^{14,15} Our study of patients undergoing lung cancer surgery also revealed that perioperative use of low-dose dexamethasone was associated with improved long-term survival.¹⁶ However, the effects of perioperative glucocorticoids on cancer outcome are conflicting; some authors even reported negative results, ie, worsened long-term survival.^{17–19}

Considering the popularity of glucocorticoid use in the perioperative period, it is necessary to further evaluate its effect on the long-term outcome of cancer patients. The purpose of this propensity-matched retrospective study was to analyze the association between perioperative glucocorticoid use and long-term survival in patients with pancreatic cancer.

Materials and Methods

This was a retrospective cohort study with propensity score-matching. The study protocol was approved by the Clinical Research Ethics Committee of Peking University Cancer Hospital (2018YJZ49). This study was conducted in accordance with the Declaration of Helsinki. Considering that the study was pure observational, the Ethics Committee agreed to waive written informed

consents; however, all patients or their family members had provided oral consents to participate in this study before collecting data.

Participants

Potential participants were screened using the electronic medical record system of the hospital. Inclusion criteria were patients who underwent radical resection for pancreatic cancer of which the diagnoses were confirmed by pathological examination from January 1, 2005 to December 31, 2016 in the first Department of Hepatic, Biliary & Pancreatic Surgery of Peking University Cancer Hospital. Exclusion criteria included the following: (1) combined primary cancer in other sites; (2) recurrent or metastatic pancreatic cancer; (3) long-term glucocorticoid therapy before surgery; (4) non-radical surgery; or (5) missing data (such as cancer size, stage, differentiation, and follow-up data, etc.).

Anesthesia, Surgery and Perioperative Management

All patients underwent general anesthesia with endotracheal intubation. Anesthesia was induced with intravenous anesthetics (propofol and/or etomidate) and opioids (fentanyl or sufentanil), and maintained with inhalational anesthetics (sevoflurane or isoflurane) and opioids (fentanyl, sufentanil, oxycodone, and/or dezocine). For some patients, non-steroidal anti-inflammatory drugs (NSAIDs, including flurbiprofen axetil and parecoxib) were administered for supplemental analgesia; epidural anesthesia was performed with local anesthetics (lidocaine and/or ropivacaine) for anesthesia maintenance and postoperative analgesia. Low-dose glucocorticoids, either dexamethasone or methylprednisolone, were administered to prevent postoperative nausea and vomiting depending on the discretion of anesthesiologists.¹¹ There were no special indications for glucocorticoid administration during the study period.

The standard median incision approach was adopted for radical resection of pancreatic cancer. Surgical procedures were performed by three chief surgeons until the end of April 2007, and by one chief surgeon thereafter. The types of surgery were decided according to the status of cancer at the discretion of the surgeons, and included pancreaticoduodenectomy, pancreatic body and tail resection plus splenectomy, and total pancreatectomy. The range of lymph node dissection was standardized for

each type of surgery. Positive surgical margin was defined when residual cancer cells were found within 1 mm of the surgical resection margins.

Postoperative patient-controlled analgesia was provided for up to 3 days. Opioids (with or without flurbiprofen axetil) were used for intravenous analgesia. Ropivacaine (with or without opioids) was used for epidural analgesia. Antiemetics including dexamethasone, 5-HT₃ receptor antagonist, and/or metoclopramide were administered when considered necessary.²⁰ Other perioperative treatments were performed according to routine practice.

Perioperative Data Collection

Patients' data were collected from the hospital's electronic medical record system. Baseline data included age, sex, height, weight, preoperative comorbidities, preoperative laboratory test results, ASA classification, and preoperative chemotherapy. Anesthesia-related data included anesthetic method, duration of anesthesia, types and doses of anesthetics, intraoperative fluid infusion and blood transfusion, postoperative analgesia, as well as perioperative use of glucocorticoids and non-steroidal anti-inflammatory drugs. Equivalent doses were calculated for opioids, NSAIDs, and glucocorticoids.^{21–25} Surgery-related data included date and type of surgery, surgical margin status, and estimated intraoperative blood loss. Postoperative data included pathological diagnoses, maximum tumor diameter, degree of cancer differentiation, Tumor-Node-Metastasis (TNM) stage of pancreatic cancer (pTNM stage), occurrence of postoperative complications, length of hospital stay, and in-hospital death.

Postoperative Long-Term Follow-Up

Patients were followed up by surgeons and specially assigned personnel after surgery. Follow-ups were performed every 6 months during the first year and once a year thereafter, in the way of outpatient review, telephone inquiry, or letter communication. During each follow-up, the results of re-examinations, the acceptance of radio-/chemotherapies and the status of living were recorded. Cancer recurrence referred to local recurrence and/or distant metastasis as confirmed by imagological examinations.²⁶ For those with cancer recurrence, the time of diagnosis was recorded; and for those who died, the time and cause of death were documented. The time of recurrence was the earliest date of imagological evidence according to which clinical diagnosis was made by surgeons. The time of death was extracted from the medical death

certificate. The recurrence-free survival and overall survival were determined according to follow-up results. Postoperative follow-up continued until patients died, lost to follow-up, or end of follow-ups.

Outcomes

The primary outcome was recurrence-free survival, ie, the duration from date of surgery until confirmed recurrence, all-cause death, loss to follow-up or end of follow-up, whichever came first. Secondary outcomes included occurrence of postoperative complications, length of stay in hospital after surgery, in-hospital mortality, and overall survival. Postoperative complications were defined as newly occurred medical events that were harmful to the patients' recovery during hospital stay and required interventional therapy, ie, class II–V on Clavien-Dindo classification.²⁷ Overall survival was defined as the duration from date of surgery until all-cause death, loss to follow-up, or end of follow-up, which ever came first.

Statistical Analysis

Sample Size Estimation

In a previous study, the median overall survival in patients with and without perioperative glucocorticoids was 46 and 22 months, respectively.¹⁵ We expected a total recruitment period of 144 months and a total follow-up period of 168 months (ie, 2 more years after the last recruitment), respectively. With the significance level set at 0.05, power at 0.8, and drop-out rate at 5%, a minimum of 99 and 98 subjects in the glucocorticoid and no-glucocorticoid groups, respectively, was needed to detect the difference. Sample size estimation was performed with the Survival-Log rank-Lakatos-Median Survival Time of the PASS 11.0 (NCSS LLC, Kaysville, UT, USA).

Data Analysis

For the purpose of analyses, patients were divided into two groups, ie, those with glucocorticoids during the intra-/postoperative period (from the day of surgery to the 3rd day after surgery) and those without. Between-group differences of baseline and intra-/postoperative variables used for propensity score-matching were compared using the absolute standardized differences (ASDs), which are defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation and calculated with the formula published by Austin.²⁸ An $ASD \geq 0.219$, ie, $1.96 \times \sqrt{(n_1 + n_2)/(n_1 \times n_2)}$, was considered imbalanced between the two groups. Regarding variables not used for propensity score matching,

continuous data were compared using the Student's *t*-test (normal distribution) or Mann–Whitney U-test (non-normal distribution); categorical data were analyzed using the chi-square test. Missing data were not replaced.

Variables that were considered clinically relevant were used for propensity score matching and were selected a priori. Baseline data included age, sex, body mass index, ASA classification, Charlson Comorbidity Index,²⁹ preoperative laboratory test results, preoperative chemotherapy, pathological diagnoses, maximum tumor diameter, Tumor-Node-Metastasis (TNM) stage of pancreatic cancer (pTNM stage), and degree of cancer differentiation. Intra- and postoperative data included date of surgery, type of surgery, status of surgical margin, duration of surgery, type of anesthesia, estimated blood loss, blood transfusion, perioperative NSAIDs, postoperative radiotherapy and chemotherapy, as well as duration of long-term follow-up. Patients were matched in a 1:1 ratio using the nearest-neighbor matching with caliper widths equal to 0.2 of the standard deviation of the logit of the propensity score.

For both full cohort and matched cohort, time-to-event variables (recurrence-free survival, overall survival, and hospital stay after surgery) were analyzed with Kaplan-Meier estimator, with differences between groups assessed with Log-rank tests. Patients who were lost during follow-up were censored at the time of last follow-ups. Categorical variables (postoperative complications, in-hospital death rate, recurrence/death rate during follow-up, and all-cause death rate during follow-up) were compared with the χ^2 test. Missing data were not replaced. Univariable associations between baseline/perioperative variables and recurrence-free/overall survival were performed with cox proportional hazard regression models. Those with $P < 0.20$ in univariate analyses and those that were considered clinically important were included in multivariable models to assess the adjusted association between perioperative glucocorticoid use and recurrence-free/overall survival.

Statistical analyses were performed with the SPSS 25.0 software (IBM SPSS Inc, Chicago, IL) and the free software package “R” version 2.15.3 including the “Matchit” and the “ROC” plugin. A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient Recruitment

A total of 241 patients underwent surgery for pancreatic cancer between January 1, 2005 and December 31, 2016.

Of these, 26 cases were excluded after data review, including 16 non-radical surgeries, 4 multiple primary cancers, and 6 with missing data (1 no pathological cancer stage, 1 no tumor differentiation grade, and 4 no follow-up data). Postoperative follow-ups were ended on August 12, 2018. Of the recruited 215 patients, 12 were lost during follow-up. All 215 cases were included in final analyses; of these, 112 received perioperative glucocorticoids and 103 did not. After propensity-matching, 64 patients remained in each group ([Figure 1](#); [Supplement Table 1](#)).

Baseline and Perioperative Data

In the full cohort, when compared with patients without glucocorticoids, those who received glucocorticoids were younger, underwent surgeries in the later period, had more negative margin, received less intraoperative crystalloid infusion, received more postoperative chemotherapy, and were followed up for a shorter duration. After propensity-matching, the two groups were well-balanced regarding baseline and perioperative variables ([Tables 1 and 2](#); [Supplement Table 2](#) and [Supplement Table 3](#)).

Postoperative Outcomes

Of all patients, the estimated 5-year recurrence-free and overall survival rates were 10.8% (95% CI 6.5–15.1) and 11.1% (95% CI 6.2–16.0), respectively. In both the full cohort and the matched cohort, recurrence-free survivals were significantly longer in patients with glucocorticoids than in those without (full cohort: median 12.0 months [95% CI 6.0–28.0] vs 6.9 months [4.2–17.0], $P < 0.001$; matched cohort: 12.0 months [5.8–26.3] vs 8.3 months [4.3–18.2], $P = 0.015$) ([Figure 2A and C](#)). As expected, the recurrence/death rate during follow-up was significantly lower in patients with glucocorticoids than in those without (full cohort: 91 (81.3%) vs 98 (95.1%), $P = 0.003$; matched cohort: 52 (81.3%) vs 61 (95.3%), $P = 0.025$). Overall survival was significantly longer in patients with glucocorticoids than in those without only in the full cohort (median 19.7 months [12.3–36.2] vs 13.9 months [8.0–23.9], $P < 0.001$) ([Figure 2B](#)), but not in the matched cohort ([Figure 2D](#)). Perioperative outcomes including postoperative complications, length of hospital stay, and in-hospital mortality did not differ between the two groups in both cohorts ([Table 3](#); [Supplement Table 4](#) and [Supplement Table 5](#)).

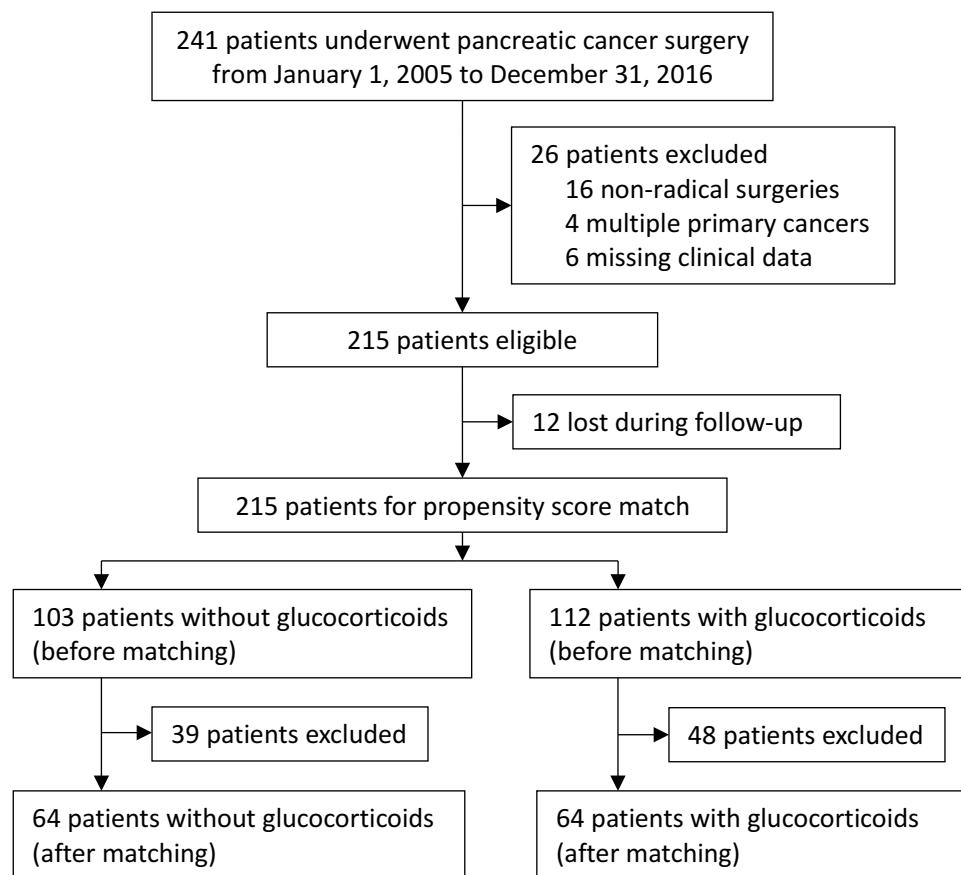


Figure 1 Flowchart of the study.

Perioperative Glucocorticoids and Recurrence-Free Survival

In the full cohort, 16 factors were included in the multivariable model, including 12 factors with $P < 0.20$ in univariable analyses (perioperative use of glucocorticoids, age ≥ 70 y, preoperative hepatorenal dysfunction, preoperative CA19-9 level, ductal adenocarcinoma, higher pTNM stage, low differentiation grade, positive surgical margin, estimated blood loss ≥ 400 mL, period of surgery, postoperative complications, and postoperative chemotherapy) and 4 factors that were considered clinically important (BMI, type of surgery, type of anesthesia, and type of inhalational anesthetics). After correction for confounding factors, perioperative glucocorticoid use was significantly associated with a prolonged recurrence-free survival (HR 0.66, 95% CI 0.48–0.92, $P = 0.015$). Among other factors, ductal adenocarcinoma (vs others), higher pTNM stage (IIB, III, IV vs IA, IB, IIA), low differentiation grade (vs medium/high grade), positive surgical margin, and estimated blood loss ≥ 400 mL were associated with shortened recurrence-free survival (Table 4; Supplement Table 6).

In the matched cohort, 16 factors were included in the multivariable model, including 12 factors with $P < 0.20$ in univariable analyses (perioperative use of glucocorticoids, age ≥ 70 y, BMI ≥ 25 kg/m², preoperative hepatorenal dysfunction, ductal adenocarcinoma, higher pTNM stage, low differentiation grade, positive surgical margin, estimated blood loss ≥ 400 mL, type of surgery, type of anesthesia, and isoflurane inhalation) and 4 factors that were considered clinically important (preoperative CA19-9 level, period of surgery, postoperative complications, and postoperative chemotherapy). After correction for confounding factors, perioperative glucocorticoid use was significantly associated with a prolonged recurrence-free survival (HR 0.54, 95% CI 0.35–0.84, $P = 0.007$). Among other factors, age ≥ 70 y (vs < 60 y), preoperative hepatorenal dysfunction, ductal adenocarcinoma (vs others), higher pTNM stage (IIB, III, IV vs IA, IB, IIA), low grade differentiation (vs medium/high grade), positive surgical margin, isoflurane inhalation (vs sevoflurane inhalation), and estimated blood loss ≥ 400 mL were associated with shortened recurrence-free survival (Table 4; Supplement Table 7).

Table 1 Baseline and Perioperative Data Used for Propensity Score Matching

Variables	All Patients (n=215)	Full Cohort (n=215)			Matched Cohort (n=128)		
		With Glucocorticoids (n=112)	Without Glucocorticoids (n=103)	ASD ^a	With Glucocorticoids (n=64)	Without Glucocorticoids (n=64)	ASD ^a
Age (year)	63 (55–70)	62 (53–69)	65 (58–71)	0.288	64 (54–73)	63 (56–68)	0.060
Male sex	125 (58.1%)	59 (52.7%)	66 (64.1%)	0.227	35 (54.7%)	39 (60.9%)	0.136
Body mass index (kg/m ²)	22.9 (21.3–24.8)	23.3 (21.4–24.7)	22.8 (21.2–25.1)	0.059	23.4 (21.8–25.2)	23.3 (21.0–25.2)	0.052
ASA grade				0.099			0.063
I	26 (9.8%)	11 (5.4%)	15 (14.6%)		6 (9.4%)	5 (7.8%)	
II	166 (81.9%)	88 (87.5%)	78 (75.7%)		54 (83.1%)	54 (83.1%)	
III	23 (8.4%)	13 (7.1%)	10 (9.7%)		4 (6.3%)	5 (7.8%)	
Charlson Comorbidity Index ^b	3 (2–3)	3 (2–3)	3 (2–3)	0.081	3 (2–3)	3 (2–3)	0.048
Preoperative lab test							
CA19-9 (U/mL)	238.9 (59.9–658.7)	185.6 (43.2–589.9)	275.1 (95.4–845.6)	0.012	170.6 (43.4–569)	276.2 (74.9–689.8)	0.102
Albumin (g/L)	39 (38–41)	39 (37–41)	39 (38–41)	0.090	39 (37–41)	39 (38–40)	0.079
Hemoglobin (g/L)	127 (122–131)	128 (123–132)	127 (121–131)	0.158	128 (123–131)	127.5 (121.0–131.0)	0.056
Preoperative chemotherapy	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	–
Pathological diagnosis				0.134			0.000
Ductal adenocarcinoma	203 (94.4%)	107 (95.5%)	96 (93.2%)		62 (96.9%)	62 (96.9%)	
Intraductal papilloma	2 (0.9%)	2 (1.8%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Adenosquamous carcinoma	1 (0.5%)	1 (0.9%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Neuroendocrine tumor	3 (1.4%)	2 (1.8%)	1 (1.0%)		1 (1.6%)	1 (1.6%)	
Mucinous adenocarcinoma	6 (2.8%)	1 (0.9%)	5 (4.9%)		1 (1.6%)	1 (1.6%)	
Maximum diameter (mm)	30 (25–40)	30 (24–39)	32 (25–42)	0.042	31 (24–39)	33 (25–40)	0.139
Pathologic TNM stage ^c				0.192			0.044
IA	4 (1.9%)	3 (2.7%)	1 (1.0%)		1 (1.6%)	1 (1.6%)	
IB	16 (7.4%)	10 (8.9%)	6 (5.8%)		6 (9.4%)	5 (7.8%)	
IIA	71 (33.0%)	42 (37.5%)	29 (28.2%)		22 (34.4%)	23 (35.9%)	
IIB	103 (47.9%)	48 (42.9%)	55 (53.4%)		32 (50.0%)	31 (48.4%)	
III	17 (7.9%)	9 (8.0%)	8 (7.8%)		3 (4.7%)	4 (6.3%)	
IV	4 (1.9%)	0 (0.0%)	4 (3.9%)		0 (0.0%)	0 (0.0%)	
Differentiation grade				0.134			0.103
Low	92 (42.8%)	45 (40.2%)	47 (45.6%)		30 (46.9%)	29 (45.3%)	
Moderate	116 (54.0%)	64 (57.1%)	52 (50.5%)		31 (48.4%)	33 (51.6%)	
High	7 (3.3%)	3 (2.7%)	4 (3.9%)		3 (4.7%)	2 (3.1%)	
Period of surgery				0.536			0.063

2005-April 2007	35 (16.3%)	10 (6.9%)	25 (24.3%)		6 (9.4%)	5 (7.8%)	
May 2007–2012	100 (46.5%)	47 (42.0%)	53 (51.5%)		35 (54.7%)	38 (59.4%)	
2013–2016	80 (37.2%)	55 (49.1%)	25 (24.3%)		23 (35.9%)	21 (32.8%)	
Type of surgery				0.118			0.080
Pancreaticoduodenectomy	150 (69.8%)	80 (71.4%)	70 (68.0%)		45 (70.3%)	43 (67.2%)	
Distal pancreatectomy	61 (28.4%)	29 (25.9%)	32 (31.1%)		18 (28.1%)	20 (31.3%)	
Total pancreatectomy	4 (1.9%)	3 (2.7%)	1 (1.0%)		1 (1.6%)	1 (1.6%)	
Pathological negative margin	190 (88.4%)	103 (92.0%)	87 (84.5%)	0.275	59 (92.2%)	59 (92.2%)	0.068
Duration of surgery (min)	300 (226–366)	300 (221–357)	300 (234–369)	0.123	300 (202–338)	298 (224–369)	0.102
Type of anesthesia				0.062			0.130
General	200 (93.0%)	105 (93.8%)	95 (92.2%)		60 (93.8%)	62 (96.9%)	
Combined epidural-general	15 (7.0%)	7 (6.3%)	8 (7.8%)		4 (6.3%)	2 (3.1%)	
Estimated blood loss (mL)	300 (200–500)	200 (160–400)	300 (200–600)	0.106	200 (160–400)	300 (200–575)	0.038
Blood transfusion	48 (22.3%)	21 (18.8%)	27 (26.2%)	0.190	11 (17.2%)	13 (20.3%)	0.050
Peroperative NSAIDs ^d	130 (60.5%)	67 (59.8%)	63 (61.2%)	0.027	43 (67.2%)	45 (70.3%)	0.034
Postoperative therapy							
Radiotherapy	22 (10.2%)	14 (12.5%)	8 (7.8%)	0.142	5 (7.8%)	7 (10.9%)	0.099
Chemotherapy	103 (47.9%)	61 (54.5%)	42 (40.8%)	0.274	29 (45.3%)	31 (48.4%)	0.078
Duration of follow-up (month)	74.0 (68.3–79.7)	65.7 (58.4–73.0)	93.8 (85.5–102.1)	0.498	72.6 (40.9–108.1)	79.5 (46.3–105.2)	0.098

Notes: ^aAn ASD ≥0.219 was considered unbalanced²⁸. ^bCalculated according to the version without age.²⁹ ^cAccording to the 8th Edition of the American Joint Committee on Cancer/Union for International Cancer Control Staging System. ^dIncludes flurbiprofen axetil and parecoxib sodium. Data are presented as median (interquartile range) or number (%). ASDs in bold indicate those of ≥0.219.

Abbreviations: ASA, American Society of Anesthesiologists; CA, cancer antigen; TNM stage, tumor-node-metastasis stage; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Baseline and Perioperative Data Not Used for Propensity Score Matching

Variables	All Patients (n=215)	Full Cohort (n=215)			Matched Cohort (n=128)		
		With Glucocorticoids (n=112)	Without Glucocorticoids (n=103)	P value	With Glucocorticoids (n=64)	Without Glucocorticoids (n=64)	P value
Preoperative comorbidities							
Previous stroke	8 (3.7%)	6 (5.4%)	2 (1.9%)	0.283	4 (6.3%)	1 (1.6%)	0.365
Coronary heart disease	15 (7.0%)	4 (3.6%)	11 (10.7%)	0.059	3 (4.7%)	8 (12.5%)	0.206
Hypertension	65 (30.2%)	29 (25.9%)	36 (35.0%)	0.181	16 (25.0%)	23 (35.9%)	0.249
Arrhythmia	47 (21.9%)	24 (21.4%)	23 (22.3%)	>0.999	17 (26.6%)	17 (26.6%)	>0.999
COPD ^a	15 (7.0%)	10 (8.9%)	5 (4.9%)	0.291	7 (10.9%)	3 (4.7%)	0.324
Asthma	5 (2.3%)	1 (0.9%)	4 (3.9%)	0.196	0 (0.0%)	2 (3.1%)	0.496
Old tuberculosis	4 (1.9%)	2 (1.8%)	2 (1.9%)	>0.999	0 (0.0%)	1 (1.6%)	>0.999
Diabetes	48 (22.3%)	27 (24.1%)	21 (20.4%)	0.623	13 (20.3%)	15 (23.4%)	0.831
Renal dysfunction ^b	1 (0.5%)	0 (0.0%)	1 (1.0%)	0.479	0 (0.0%)	0 (0.0%)	>0.999
Liver dysfunction ^c	102 (47.4%)	57 (50.9%)	45 (43.7%)	0.339	32 (50.0%)	29 (45.3%)	0.724
Duration of anesthesia (min)	332 (267–402)	334 (265–386)	331 (270–409)	0.491	332 (240.5–384)	325.5 (256–403)	0.567
Intravenous anesthetics							
Propofol dose (mg)	150 (100–160)	150 (100–160)	150 (50–180)	0.436	150 (100–160)	140 (50–180)	0.102
Etomidate dose (mg)	0 (0–10)	0 (0–10)	0 (0–15)	0.147	0 (0–10)	5 (0–18)	0.056
Intraoperative fluid							
Crystalloids (mL)	1800 (1400–2250)	1625 (1300–2200)	2000 (1500–2600)	0.004	1700 (1260–2075)	1825 (1500–2450)	0.063
Artificial colloid (mL) ^d	1000 (1000–1500)	1000 (1000–1500)	1000 (800–1500)	0.806	1000 (1000–1500)	1000 (650–1000)	0.184
Blood transfused (mL)	0 (0–0)	0 (0–0)	0 (0–400)	0.197	0 (0–0)	0 (0–0)	0.712
Perioperative medication							
Inhalational anesthetics	215 (100.0%)	112 (100%)	103 (100%)	—	64 (100%)	64 (100%)	—
Sufentanil equivalent, µg ^e	255 (120–320)	270 (140–320)	255 (85–320)	0.093	252.5 (138.5–320)	252.5 (153–323)	0.791
FA equivalent, mg ^f	100 (0–300)	100 (0–387.5)	100 (0–300)	0.983	250 (0–400)	300 (0–300)	0.918
Glucocorticoids ^g	112 (52.1%)	112 (100.0%)	—	—	64 (100.0%)	—	—
DXM equivalent (mg) ^h	5 (0–10)	10 (6.75–10)	—	—	10 (10–10)	—	—

Notes: Data are median (interquartile range) or number (%). P values in bold indicate those of <0.05. ^aInclude chronic bronchitis and emphysema. ^bSerum creatinine >133µmol/L. ^cAlanine transaminase, aspartate transaminase and/or total bilirubin 2 times higher than the upper normal limit. ^dIncludes hydroxyethyl starch 130/0.4, hydroxyethyl starch 200/0.5, and succinylated gelatin. ^e1 mg morphine (iv) = 15 µg fentanyl = 1.5 µg sufentanil = 1 mg oxycodone = 1 mg dezocine. ^fIncludes flurbiprofen axetil and parecoxib sodium. 40 mg parecoxib sodium = 50 mg flurbiprofen axetil. ^gIncludes methylprednisolone and dexamethasone. ^h1 mg methylprednisolone = 0.2 mg dexamethasone. ²⁵

Abbreviations: FA, flurbiprofen axetil; DXM, dexamethasone.

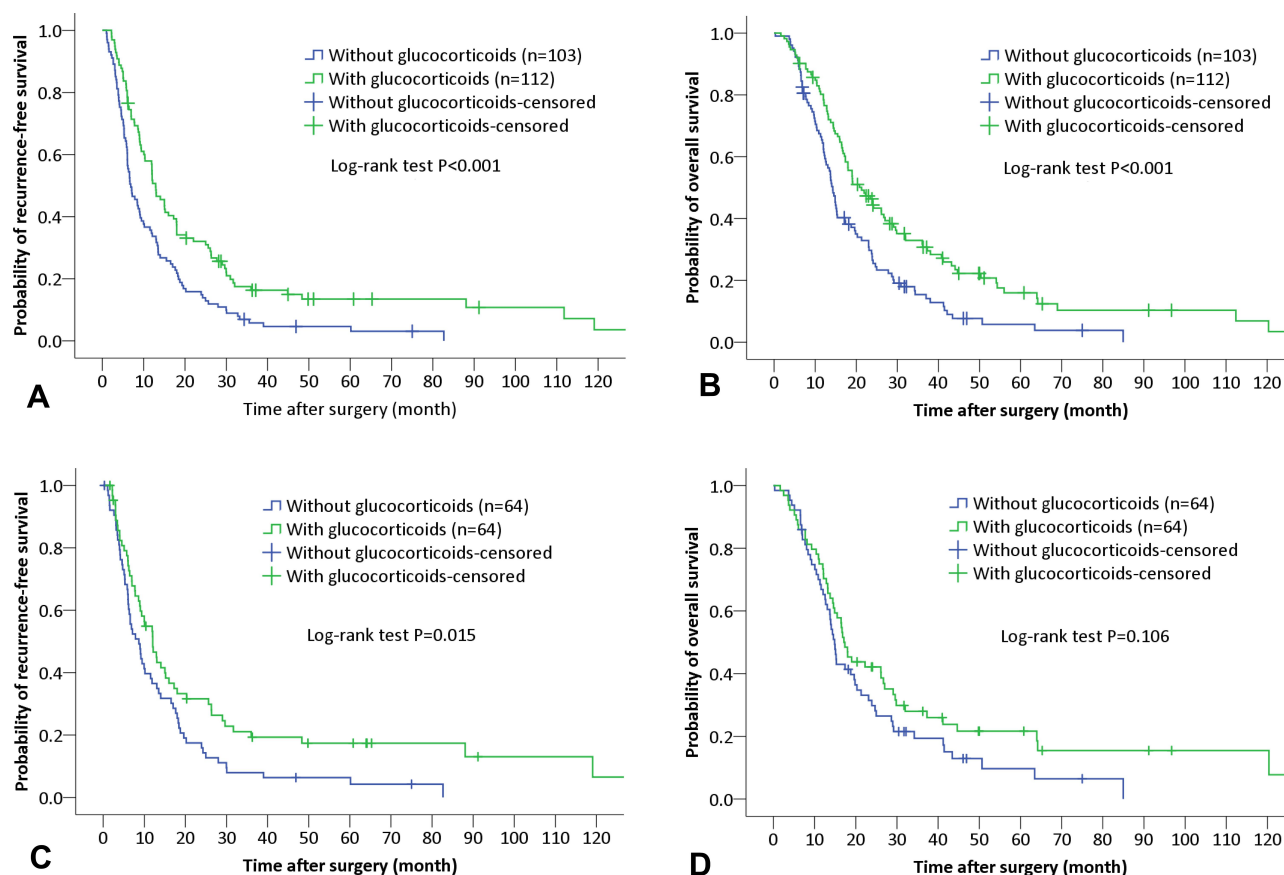


Figure 2 Survival curves of patients with or without perioperative glucocorticoids after pancreatic cancer surgery. In the full cohort, the recurrence-free survival (A) and overall survival (B) were significantly longer in patients with glucocorticoids than in those without (Log-rank test, both $P<0.001$). In the matched cohort, the recurrence-free survival (C) was significantly longer in patients with glucocorticoids than in those without (Log-rank test $P=0.015$); the overall survival (D) did not differ significantly between the two groups. +, subjects who were censored.

Discussion

In this retrospective study with propensity score-matching, 215 patients after pancreatic cancer surgery were followed up for a median of 74.0 months. In both the full cohort and the matched cohort, recurrence-free survival was significantly longer in patients with perioperative glucocorticoids than in those without; perioperative glucocorticoids were significantly associated with prolonged recurrence-free survival after correction for confounding factors.

Surgical resection is the primary treatment for patients with pancreatic cancer. However, even after radical resection and modern chemotherapy, long-term prognosis of pancreatic cancer patients remains poor. According to recent studies, the median recurrence-free survival after pancreatic cancer surgery (and chemotherapy) was 6.7–22.9 months, the median overall survival was 10.9–54.4 months, and the 5-year survival rate was 7.3–44.1%.^{3,4} In the present study, the median recurrence-free survival was 9.4 months (95% CI

5.1–20.3), the median overall survival was 16.8 months (95% CI 10.4–29.2), and the 5-year survival rate was 11.1% (95% CI 6.2–16.0). The results of our patients were all within the ranges of previous reports.

Glucocorticoids have long been used as the first-line therapy in patients with hematologic malignancies.³⁰ However, the reported effects of perioperative glucocorticoids on long-term outcomes after cancer surgery vary widely and may be cancer-dependent. For example, long-term follow-up of patients after colorectal cancer surgery showed that perioperative dexamethasone was associated with an increased risk of cancer recurrence.¹⁷ Whereas studies of patients undergoing surgeries for ovarian and breast cancers did not find any significant effects of antiemetic dose dexamethasone on long-term survival.^{18,19} On the other hand, a retrospective study of lung cancer patients showed improved recurrence-free and overall survival with perioperative glucocorticoids.¹⁶ Studies involving pancreatic cancer patients were limited. In two

Table 3 Postoperative and Long-Term Outcomes

Variables	All Patients (n=215)	Full Cohort (n=215)			Matched cohort (n=128)		
		With Glucocorticoids (n=112)	Without Glucocorticoids (n=103)	P value	With Glucocorticoids (n=64)	Without Glucocorticoids (n=64)	P value
Primary endpoint Recurrence-free survival (month) ^a	9.4 (5.1–20.3)	12.0 (6.0–28.0)	6.9 (4.2–17.0)	<0.001	12.0 (5.8–26.3)	8.3 (4.3–18.2)	0.015
Secondary endpoints							
Postoperative complications ^b	51 (23.7%)	22 (19.6%)	29 (28.2%)	0.152	14 (21.9%)	19 (29.7%)	0.419
Length of hospital stay (day)	16.0 (8.0–27.0)	16.0 (13.4–18.6)	17.0 (11.3–22.7)	0.754	17.0 (12.7–21.3)	13.0 (8.8–17.2)	0.360
In-hospital death	2 (0.9%)	1 (1.0%)	1 (0.9%)	>0.999	0 (0.0%)	0 (0.0%)	—
Recurrence/death during follow-up ^a	189 (87.9%)	91 (81.3%)	98 (95.1%)	0.003	52 (81.3%)	61 (95.3%)	0.025
All-cause death during follow-up ^c	182 (84.7%)	90 (80.4%)	92 (89.3%)	0.088	51 (79.7%)	56 (87.5%)	0.340
Overall survival (month) ^c	16.8 (10.4–29.2)	19.7 (12.3–36.2)	13.9 (8.0–23.9)	<0.001	17.2 (11.3–31.9)	14.7 (9.0–27.7)	0.106

Notes: Data are median (95% CI), number (%), or median (interquartile range). P values in bold indicate those of <0.05. ^aLocal recurrence and/or distant metastasis as confirmed by imaging examination.²⁶ or all-cause death.^b Newly occurred medical events that were harmful to the patients' recovery during postoperative hospitalization and required interventional therapy, ie, class II–V on Clavien-Dindo classification. ^cAll-cause death.

retrospective studies of patients after pancreatic cancer surgery, perioperative low-dose dexamethasone (4–10 mg) was associated with the prolonged overall survival.^{14,15} In the present study, 52.1% of our patients received glucocorticoid (median equivalent dose of dexamethasone 10 mg) during anesthesia and/or early postoperative period. Our results also showed that, in both the full cohort and the matched cohort, perioperative glucocorticoids were associated with improved recurrence-free survival after surgery; these were in line with the above studies in pancreatic cancer patients.^{14,15}

The potential mechanisms by which glucocorticoids may improve long-term outcomes after pancreatic cancer surgery remain unclear, but may be related to its anti-inflammatory and immunomodulatory effects. Inflammation, especially chronic inflammation, might play an important role in the occurrence and development of pancreatic cancer.⁵ Cytokines produced by immune and cancer cells can not only enhance cancer invasiveness but also produce immunosuppression which promote cancer cells to escape from immune surveillance.⁵ During the perioperative period, surgery-related inflammation is associated with profound immunosuppression, which may accelerate cancer recurrence and metastasis.³¹ Glucocorticoids have a broad-spectrum anti-inflammatory effect.³² In a randomized controlled trial by Kim et al,³³ a single-dose

dexamethasone (10 mg) significantly relieved the degree of inflammation within 24 hours after uterine arterial embolization. Along with the anti-inflammatory effect, glucocorticoids can modulate immune function by suppressing the Th1-cellular immunity axis and augmenting the Th2-mediated humoral immunity, which may provide protection against surgical stress.^{28,34} A study in healthy volunteers showed that the anti-inflammatory and immunomodulatory effects of a single-dose dexamethasone (8 mg) lasts for at least 24 hours.¹²

Concerns regarding perioperative glucocorticoid use include the possibility of increased postoperative infection and anastomotic leak, as well as elevated blood glucose which is also associated with increased postoperative complications.^{35,36} However, these adverse events are mainly observed in patients with prolonged glucocorticoid use,³³ but not in those given only short-term therapy.³⁷ On the contrary, a randomized controlled trial reported that perioperative hydrocortisone (100 mg every 8 hours for 3 days) reduced major complications after pancreaticoduodenectomy.³⁸ In a recent retrospective cohort study, patients who received a single-dose dexamethasone developed less infectious complications after pancreatic cancer surgery.¹⁵ Results of the present study also showed that perioperative use of antiemetic

Table 4 Cox Regression Proportional Hazard Survival: Multivariable Model for Full Cohort and Matched Cohort

Factors ^a	Full Cohort (n=215)				Matched Cohort (n=128)			
	Recurrence-Free Survival		Overall Survival		Recurrence-Free Survival		Overall Survival	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Perioperative glucocorticoids ^b								
No								
Yes	0.66 (0.48–0.92)	0.015	0.75 (0.53–1.04)	0.084	0.54 (0.35–0.84)	0.007	0.70 (0.45–1.11)	0.127
Age (y)								
<60								
60–69	0.93 (0.65–1.34)	0.701	1.01 (0.70–1.46)	0.950	0.85 (0.52–1.40)	0.528	0.88 (0.53–1.47)	0.628
≥70	1.28 (0.86–1.90)	0.232	1.33 (0.89–2.00)	0.161	1.94 (1.11–3.38)	0.020	1.72 (0.97–3.05)	0.062
Body mass index (kg/m ²)								
≤24.9								
≥25	0.79 (0.55–1.13)	0.190	0.83 (0.57–1.21)	0.336	0.67 (0.41–1.09)	0.107	0.71 (0.42–1.18)	0.185
Hepatorenal dysfunction								
No								
Yes	1.08 (0.74–1.58)	0.702	1.10 (0.75–1.61)	0.642	1.87 (1.10–3.19)	0.021	1.36 (0.81–2.28)	0.248
Preoperative CA19-9								
<240 U/mL								
≥240 U/mL	1.28 (0.93–1.76)	0.126	1.07 (0.78–1.48)	0.672	1.34 (0.86–2.08)	0.202	1.37 (0.86–2.18)	0.183
Pathological diagnosis								
Others ^c								
Ductal adenocarcinoma	2.55 (1.14–5.68)	0.022	2.09 (0.98–4.46)	0.058	5.68 (1.43–22.73)	0.014	6.06 (1.61–22.73)	0.008
pTNM stage ^d								
IA, IB, IIA								
IIB, III, IV	1.50 (1.08–2.09)	0.016	1.68 (1.19–2.39)	0.004	1.79 (1.16–2.77)	0.009	1.59 (1.01–2.50)	0.045
Differentiation grade								
Moderate and high								
Low	2.15 (1.53–3.02)	<0.001	2.01 (1.43–2.84)	<0.001	1.98 (1.25–3.13)	0.003	1.75 (1.09–2.80)	0.021
Period of surgery								
2005–April 2007								
May 2007–2012	1.09 (0.63–1.89)	0.763	0.98 (0.57–1.68)	0.937	0.75 (0.30–1.84)	0.524	0.93 (0.39–2.25)	0.879
2013–2016	1.14 (0.61–2.12)	0.682	0.78 (0.43–1.41)	0.413	0.55 (0.21–1.48)	0.238	0.54 (0.20–1.45)	0.223
Type of surgery								
Pancreaticoduodenectomy/ total pancreatectomy								
Distal pancreateosplenectomy	0.82 (0.50–1.34)	0.435	0.77 (0.48–1.23)	0.271	1.27 (0.69–2.33)	0.444	0.96 (0.53–1.76)	0.902
Margin status								
Negative								
Positive	1.70 (1.00–2.90)	0.049	1.95 (1.14–3.36)	0.015	2.74 (1.31–5.70)	0.007	2.74 (1.24–6.02)	0.012
Type of anesthesia								
General								
Combined	0.69 (0.33–1.44)	0.320	0.59 (0.30–1.17)	0.129	0.48 (0.14–1.57)	0.476	0.95 (0.31–2.92)	0.922
Inhalational anesthetics								
Sevoflurane								
Isoflurane	1.35 (0.94–1.92)	0.102	1.62 (1.13–2.32)	0.008	1.68 (1.02–2.76)	0.042	1.85 (1.13–3.02)	0.014

(Continued)

Table 4 (Continued).

Factors ^a	Full Cohort (n=215)				Matched Cohort (n=128)			
	Recurrence-Free Survival		Overall Survival		Recurrence-Free Survival		Overall Survival	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Estimated blood loss								
<400 mL								
≥400 mL	1.59 (1.08–2.35)	0.019	1.77 (1.20–2.59)	0.004	1.89 (1.09–3.26)	0.023	2.02 (1.17–3.48)	0.011
Postoperative complications ^e								
No								
Yes	1.11 (0.77–1.60)	0.578	1.32 (0.91–1.91)	0.149	1.01 (0.61–1.65)	0.983	1.27 (0.77–2.10)	0.352
Postoperative chemotherapy								
No								
Yes	0.77 (0.56–1.05)	0.097	0.68 (0.49–0.95)	0.022	0.76 (0.50–1.15)	0.193	0.67 (0.43–1.04)	0.074

Notes: ^aFactors with $P < 0.20$ in univariable analyses and those that were considered clinically important were included in multivariable analyses. ^bIncludes dexamethasone and methylprednisolone. ^cIncludes intraductal papilloma, adeno-squamous carcinoma, neuroendocrine tumor, and mucinous adenocarcinoma. ^dAccording to the American Joint Committee on Cancer 8th Edition Cancer Staging System. ^eDefined as new-onset conditions that required medical intervention. Includes delayed gastric emptying, biliary leak, pancreatic leak, chylous leak, surgical site infection, atelectasis, pleural effusion, pulmonary infection, acute respiratory failure, and deep vein thrombosis.

Abbreviations: RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. P values in bold indicate those of < 0.05 .

dose glucocorticoids did not increase complications after surgery for pancreatic cancer.

It is well known that perioperative blood transfusion is associated with shortened long-term survival after cancer (including pancreatic cancer) surgery.^{39,40} As a matter of fact, high volume intraoperative blood loss is also associated with worse outcomes including increased postoperative complications⁴¹ and deteriorated long-term outcomes.^{42,43} For example, in a retrospective study of patients with stage II/III gastric cancer, intraoperative blood loss of > 330 mL was associated with early recurrence after surgery.⁴² In a retrospective study of pancreatic cancer patients, patients with massive intraoperative blood loss had shorter overall survival and recurrence-free survival after surgery, although the associations were no longer significant after the correction for confounding factors.⁴³ In the present study, we did not find significant associations between perioperative blood transfusion and long-term outcomes after pancreatic cancer surgery, possibly due to the small number of patients receiving blood transfusions. However, we found that high volume intraoperative blood loss (≥ 400 mL) was associated with shortened recurrence-free and overall survival, which is consistent with previous studies.

The impacts of inhalational anesthetics on long-term outcomes after cancer surgery attract much attention. Available studies (mainly retrospective) indicated that volatile inhalational anesthesia was associated with shortened long-term survival after cancer surgery when compared with propofol

intravenous anesthesia,⁴⁴ possibly due to the enhanced immunosuppression and the upregulated hypoxia-inducible-factor-1 and matrix metalloproteinases.⁴⁵ However, the effects of different inhalational anesthetics might be different.⁴⁵ In a study of patients undergoing cytoreductive surgery for ovarian cancer, desflurane anesthesia was associated with delayed recurrence compared with sevoflurane.⁴⁶ In the present study, isoflurane anesthesia was associated with shortened overall and recurrence-free survival when compared with sevoflurane. The effects of different inhalational anesthetics on the prognosis of patients undergoing cancer surgery require further studies. Our study also found that the pathological diagnosis of ductal adenocarcinoma, high-grade TNM stage, low degree of cancer differentiation, and positive surgical margin were associated with shorter survival; whereas postoperative chemotherapy was associated with longer survival. These results are consistent with previous reports.^{14,15}

In addition to the retrospective nature, there are other limitations of the present study. Firstly, patients included in this study underwent surgery over a period of 12 years. The chief surgeons changed during this period, and so were some routine clinical practices. For example, glucocorticoids were used more frequently and the number of surgical cases were higher in recent years. These might produce bias. In the present study, the period of surgery was used for propensity score-matching and was included in the multivariable model in order to correct for its

potential confounding effects.⁴⁷ Secondly, only 15 cases (7.0%) received combined epidural block during general anesthesia in our patients. This limited our ability to detect any effects of epidural block on the outcome of pancreatic cancer patients, which was suggested by previous studies.¹⁴ Lastly, as a single-center study, the generalizability of our results may be limited.

Conclusions

In summary, results of this retrospective study with propensity score-matching showed that perioperative use of low-dose glucocorticoids was associated with improved recurrence-free survival in patients undergoing radical surgery for pancreatic cancer. Considering the widespread use of glucocorticoids in the perioperative period, prospective studies are urgently needed to clarify its effect on long-term outcomes after pancreatic cancer surgery.

Abbreviations

TNM, tumor-node-metastasis; OS, overall survival; RFS, recurrence-free survival.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study protocol was approved by the Clinical Research Ethics Committee of Peking University Cancer Hospital (2018YJZ49).

Consent for Publication

Not applicable.

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Author Contributions

DXW conceived the study and was responsible for study supervision. YXZ, DLM and DXW designed the study. YXZ and KMJ recruited patients, collected baseline and

perioperative data, and performed postoperative follow-ups. YXZ, DLM, KMJ, XYL and DXW analyzed and interpreted all the data. XYL contributed to statistical analyses. YXZ drafted the manuscript. DXW and DLM critically revised the manuscript. DXW supplied administrative, technical, and material support. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

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