Perioperative glucocorticoids are associated with improved long-term survival after pancreatic cancer surgery: A retrospective cohort study

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Research article

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Abstract

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

Methods In this retrospective cohort study, 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 for tumor recurrence and survival. The primary outcome was the overall survival (OS); the secondary outcome was the recurrence-free survival (RFS). A multivariable Cox proportional hazard model was used to analyze the influence of perioperative glucocorticoid use on OS and RFS after correction for confounding factors.

Results A total of 215 patients after radical surgery for pancreatic cancer 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). Both OS and RFS were significantly longer in patients with glucocorticoids than in those without (for OS: median 19.7 months [95% CI 12.3-36.2] vs. 13.9 months [8.0-23.9], P=0.001; for RFS: 12.0 months [6.0-28.0] vs. 6.9 months [4.2-17.0], P=0.002). After correction for confounding factors, perioperative glucocorticoids were significantly associated with prolonged OS (HR 0.692, 95% CI 0.499-0.959, P=0.027) and RFS (HR 0.634, 95% CI 0.459-0.878, P=0.006).

Conclusions Perioperative use of low-dose glucocorticoids may improve long-term survival in patients undergoing radical surgery for pancreatic cancer.

Background

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 China 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 patients to achieve prolonged survival [3]. However, recent evidence showed that, even after radical resection and modern adjuvant chemotherapy, the clinical outcome of pancreatic cancer remains poor, with a median overall survival time of 28–54 months [4]. Recurrence and metastasis are the main reasons leading to short survival of patients 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]. What's more, surgery-related inflammation will 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 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, i.e., 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 retrospective study was to analyze the association between perioperative glucocorticoid use and long-term survival in patients with pancreatic cancer.

Methods

This was a retrospective cohort study. The study protocol was approved by the Clinical Research Ethics Committee of Beijing Cancer Hospital (2018YJZ49). 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 Beijing 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 (5-10 mg) or methylprednisolone (10-80 mg), 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.

No patient received medical therapy for cancer before surgery, including neoadjuvant chemotherapy. The standard median incision approach for radical resection of pancreatic cancer was implemented. 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 3 days. Opioids (with or without flurbiprofen axetil) was used for intravenous analgesia. Ropivacaine (with or without opioids) was used for epidural analgesia. Antiemetics including dexamethasone (5-10 mg), 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 living status and the recurrence of cancer were confirmed, and the acceptance of radio-/chemotherapy were recorded. For those with cancer recurrence, the time of diagnosis was recorded; and for those who died, the time and cause of death were documented. Cancer recurrence referred to local recurrence and/or distant metastasis as confirmed by imagological examination [26]. 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 overall survival (OS) and recurrence-free survival (RFS) 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 OS after surgery, i.e., the duration from the date of surgery until the patients' death or loss to follow-up or the end of follow-up. Secondary outcome was RFS after surgery, i.e. the duration from the date of surgery until and the confirmed recurrence, the patients' death or loss to follow-up, or the end of follow-up, whichever 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 (i.e., 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-Logrank-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, i.e., those with glucocorticoids during the perioperative period (from the day of surgery to the 3rd day after surgery) and those without. Numeric variables were compared with unpaired t test or Mann-Whitney u test. Categorial variables were compared with the $\chi 2$ test. Time-to-event variables were analyzed with Kaplan-Meier estimator, with differences between groups assessed with log-rank tests. Univariable associations between baseline and perioperative variables and OS or RFS were performed with Kaplan-Meier survival analyses. The factors with $P<0.20$ in univariable analyses and those that were considered clinically important were included in the multivariable Cox proportional hazard models to identify the effects of glucocorticoids on postoperative OS and RFS after correction for confounding factors. Data analyses were performed with the SPSS 25.0 software (IBM SPSS Inc, Chicago, IL). A two-sided $P<0.05$ was considered statistically significant.

Results

The median OS was significantly longer (19.7 months [95% CI 12.3-36.2] vs. 13.9 months [95% CI 8.0-23.9], P=0.001) and the 5-year OS rate was significantly higher (16.0% [95% CI 8.0-24.0] vs. 5.8% [95% CI 0.5-11.1], P<0.001) in patients with glucocorticoids than in those without. Also the median RFS was

significantly longer (12.0 months [95% CI 6.0-28.0] vs. 6.9 months [95% CI 4.2-17.0]; P=0.002) and the 5-year RFS rate was significantly higher (16.4% [95% CI 9.1-23.7] vs. 4.9% [95% CI 0.6-9.2], P<0.001) in patients with glucocorticoids than in those without. Perioperative outcomes including postoperative complications and length of hospital stay after surgery did not differ between the two groups (Table 2, Supplemental Table 4).

Factors in association with overall and recurrence-free survival

Univariable analyses identified 14 factors that might be associated with OS or RFS after surgery (P<0.20), including age, history of hypertension, preoperative hepatorenal dysfunction, preoperative CA19-9 level, pathologic diagnosis, pTNM stage, cancer differentiation grade, period of surgery, surgical margin status, type of inhalational anesthetics, perioperative glucocorticoids, estimated intraoperative blood loss, postoperative complications, and postoperative chemotherapy (Table 3). There were no collinearities among these factors.

Glucocorticoids and postoperative overall survival

After correction for confounding factors in a multivariable model, perioperative administration of glucocorticoids was significantly associated with a prolonged OS after surgery (HR 0.692, 95% CI 0.499-0.959, P=0.027). Among other factors, pathological diagnosis of ductal adenocarcinoma (vs. others: HR 2.088, 95% CI 1.026-4.237; P=0.042), high pTNM stage (IIB,III,IV vs. IA,IB,IIA: HR 1.628, 95% CI 1.138-2.329; P=0.008), low cancer differentiation (vs. medium/high: HR 1.950, 95% CI 1.394-2.729; P<0.001), estimated intraoperative blood loss ≥400 ml (HR 1.566, 95% CI 1.114-2.201; P=0.010), and isoflurane inhalation (vs. sevoflurane inhalation: HR 1.578, 95% CI 1.105-2.255; P=0.012) were associated with shortened OS; whereas negative surgical margin (HR 0.531, 95% CI 0.310-0.909; P=0.021) and postoperative chemotherapy (HR 0.700, 95% CI 0.504-0.972; P=0.033) were associated with prolonged OS after surgery (Table 4).

Glucocorticoids and postoperative recurrence-free survival

After correction for confounding factors in a multivariable model, perioperative administration of glucocorticoids was significantly associated with a prolonged RFS after surgery (HR 0.634, 95% CI 0.459-0.878, P=0.006). Among other factors, pathological diagnosis of ductal adenocarcinoma (vs. others: HR 2.387, 95% CI 1.112-5.128; P=0.026), higher pTNM stage (IIB,III,IV vs. IA, IB, IIA: HR 1.411, 95% CI 1.009-1.973; P=0.044), low cancer differentiation (vs. medium/high: HR 2.159, 95% CI 1.547-3.013; P<0.001), and estimated intraoperative blood loss ≥400 ml (HR 1.488, 95% CI 1.052-2.103; P=0.025) were associated with shortened RFS; whereas negative surgical margin (HR 0.587, 95% CI 0.350-0.987; P=0.044) was associated with prolonged RFS after surgery (Table 4).

Discussion

In this retrospective study, 215 patients after pancreatic cancer surgery were followed up for a median of 74.0 months. The results showed that patients with perioperative glucocorticoids had significantly longer overall and recurrence-free survival when compared with those without. After correction for confounding factors, perioperative use of glucocorticoids was still significantly associated with prolonged overall and recurrence-free survival after surgery.

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 [27]. However, the reported effects of perioperative glucocorticoids on the 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, our retrospective study of lung cancer patients showed improved recurrence-free and overall survival with perioperative glucocorticoids [16]. Studies regarding pancreatic cancer patients were limited. In two 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 perioperative glucocorticoid (median equivalent dose of dexamethasone 10 mg). In line with the above studies in pancreatic cancer patients, our results also showed that perioperative glucocorticoids were associated with improved long-term survival after surgery.

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 can accelerate cancer recurrence and metastasis [28]. Glucocorticoids have a broad-spectrum anti-inflammatory effect [29]. In a randomized controlled trial by Kim et al., a single-dose dexamethasone (10 mg) significantly relieved the degree of inflammation within 24 hours after uterine arterial embolization [30]. 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, 31]. 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 [32, 33]. However, these adverse events are mainly observed in patients with prolonged glucocorticoid use [33], but not in those who received only short-term therapy [34]. On the contrary, a randomized controlled trial reported that perioperative hydrocortisone (100 mg every 8 hours for 3 days) reduced major complications after pancreaticoduodenectomy [35]. 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 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 [36, 37]. As a matter of fact, high volume intraoperative blood loss is also associated with worse outcomes including increased postoperative complications [38] and deteriorated long-term outcomes [39, 40]. 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 [39]. 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 [40]. 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 long-term 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 [41]; possibly due to the enhanced immunosuppression and the upregulated hypoxia-inducible-factor-1 and matrix metalloproteinases [42]. However, the effects of different inhalational anesthetics might be different [42]. In a study of patients undergoing cytoreductive surgery for ovarian cancer, desflurane anesthesia was associated with delayed recurrence compared with sevoflurane [43]. In the present study, isoflurane anesthesia was associated with shortened overall survival compared with sevoflurane. The effects of different inhalational anesthetics on the prognosis of patients undergoing cancer surgery required further studies. Our study also found that the pathological diagnosis of ductal adenocarcinoma, high grade TNM stage and low degree of cancer differentiation were associated with shorter survival; whereas negative surgical margin and postoperative chemotherapy were associated with longer survival. These results are consistent with previous studies [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 had changed during this period, and so were 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 included in the multivariable model in order to correct for its potential confounding effects [44]. 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 showed that perioperative use of low-dose glucocorticoids was associated with improved long-term survival in patients undergoing radical surgery for pancreatic cancer. Considering the popularity of glucocorticoid use 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

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

None.

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Authors' 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 analysed 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 read and approved the final manuscript.

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References

[1]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

[2]. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115-132.

[3]. Strobel O, Neoptolemos J, Jäger D, Büchler MW. Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol. 2019;16:11-26.

[4]. Niesen W, Hank T, Büchler M, Strobel O. Local radicality and survival outcome of pancreatic cancer surgery. Ann Gastroenterol Surg. 2019;3:464-475.

[5]. Padoan A, Plebani M, Basso D. Inflammation and pancreatic cancer: focus on metabolism, cytokines, and immunity. Int J Mol Sci. 2019;20:pii: E676.

[6]. Li Y, Wang B, Zhang LL, He SF, Hu XW, Wong GT, et al. Dexmedetomidine combined with general anesthesia provides similar intraoperative stress response reduction when compared with a combined

general and epidural anesthetic technique. Anesth Analg. 2016;122:1202-1210.

[7]. Duan P, Liu Y, Li J. The comparative efficacy and safety of topical non-steroidal anti-inflammatory drugs for the treatment of anterior chamber inflammation after cataract surgery: a systematic review and network meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2017; 255:639-649.

[8]. Grandhi RK, Lee S, Abd-Elsayed A. The relationship between regional anesthesia and cancer: A Metaanalysis. Ochsner J. 2017;17:345-361.

[9]. Forget P, Machiels JP, Coulie PG, Berliere M, Poncelet AJ, Tombal B, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. Ann Surg Oncol. 2013;20 Suppl 3:S650-S660.

[10]. Zhang DF, Su X, Meng ZT, Li HL, Wang DX, Li XY, et al. Impact of dexmedetomidine on long-term outcomes after noncardiac surgery in elderly: 3-Year follow-up of a randomized controlled trial. Ann Surg. 2019; 270:356-363.

[11]. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118:85-113.

[12]. Bain CR, Draxler DF, Taylor R, Wallace S, Gouldthorpe O, Corcoran TB, et al. The early in-vivo effects of a single anti-emetic dose of dexamethasone on innate immune cell gene expression and activation in healthy volunteers. Anaesthesia. 2018;73:955-966.

[13]. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. EMT and dissemination precede pancreatic tumor formation. Cell. 2012;148:349-361.

[14]. Call TR, Pace NL, Thorup DB, Maxfield D, Chortkoff B, Christensen J, et al. Factors associated with improved survival after resection of pancreatic adenocarcinoma: a multivariable model. Anesthesiology. 2015;122: 317-324.

[15]. Sandini M, Ruscic KJ, Ferrone CR, Warshaw AL, Qadan M, Eikermann M, et al. Intraoperative dexamethasone decreases infectious complications after pancreaticoduodenectomy and is associated with long-term survival in pancreatic cancer. Ann Surg Oncol. 2018;25:4020-4026.

[16]. Huang WW, Zhu WZ, Mu DL, Ji XQ, Nie XL, Li XY, et al. Perioperative management may improve long-term survival in patients after lung cancer surgery: a retrospective cohort study. Anesth Analg. 2018;126:1666-1674.

[17]. Singh PP, Lemanu DP, Taylor MH, Hill AG. Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. Br J Anaesth. 2014;113 Suppl 1:i68-i73.

[18]. Kim MH, Kim DW, Park S, Kim JH, Lee KY, Hwang J, et al. Single dose of dexamethasone is not associated with postoperative recurrence and mortality in breast cancer patients: a propensity-matched cohort study. BMC Cancer. 2019;19:251.

[19]. De Oliveira GS Jr, McCarthy R, Turan A, Schink JC, Fitzgerald PC, Sessler DI. Is dexamethasone associated with recurrence of ovarian cancer? Anesth Analg. 2014;118:1213-1218.

[20]. Zhu M, Zhou C, Huang B, Ruan L, Liang R. Granisetron plus dexamethasone for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery: A meta-analysis. J Int Med Res. 2017;45:904-911.

[21]. Opioids, in LiverTox: clinical and research information on drug-induced liver injury. 2012, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD).

[22]. Silvasti M, Rosenberg P, Seppälä T, Svartling N, Pitkänen M. Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. Acta Anaesthesiol Scand. 1998;42:576-580.

[23]. Downing JW, Brock-Utne JG, Barclay A,Schwegmann IL. WY 16225 (dezocine), a new synthetic opiate agonist-antagonist and potent analgesic: comparison with morphine for relief of pain after lower abdominal surgery. Br J Anaesth.1981;53:59-64.

[24]. Luo X, Lv F, Peng M. Analgesic effect of different dosage of Flurbiprofen axetil in laparoscopic cholecystectomy in comparison with other analgesic drugs. Pak J Pharm Sci. 2017;30:1895-1898.

[25]. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med. 1977;63:200-207.

[26]. Chouliaras K, Newman NA, Shukla M, Swett KR, Levine EA, Sham J, et al. Analysis of recurrence after the resection of pancreatic neuroendocrine tumors. J Surg Oncol. 2018;118: 416-421.

[27]. Frankfurt O, Rosen ST. Mechanisms of glucocorticoid-induced apoptosis in hematologic malignancies: updates. Curr Opin Oncol. 2004;16:553-563.

[28]. O'Dwyer MJ, Owen HC, Torrance HD. Torrance, The perioperative immune response. Curr Opin Crit Care. 2015;21:336-342.

[29]. Barnes PJ. Glucocorticosteroids. Handb Exp Pharmacol. 2017;237:93-115.

[30]. Kim SY, Koo BN, Shin CS, Ban M, Han K, Kim MD. The effects of single-dose dexamethasone on inflammatory response and pain after uterine artery embolisation for symptomatic fibroids or adenomyosis: a randomised controlled study. Bjog. 2016;123:580-587.

[31]. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci. 2004;1024:138-146.

[32]. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg. 2013;257:8-14.

[33]. Slieker JC, Komen N, Mannaerts GH, Karsten TM, Willemsen P, Murawska M, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. Arch Surg.2012;147:447-452.

[34]. Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of perioperative glucocorticoids in elective noncardiac surgery: a systematic review and meta-analysis. Anesthesiology.2017; 126:234-248.

[35]. Laaninen M, Sand J, Nordback I, Vasama K, Laukkarinen J. Perioperative hydrocortisone reduces major complications after pancreaticoduodenectomy: a randomized controlled trial. Ann Surg.2016; 264:696-702.

[36]. Pushan Z, Manbiao C, Sulai L, Jun L, Ruidong Z, Hanshen Y. The impact of perioperative blood transfusion on survival and recurrence after radical prostatectomy for prostate cancer: A systematic review and meta-analysis. J Cancer Res Ther. 2018;14(Supplement):S701-S707.

[37]. Mavros MN, Xu L, Maqsood H, Gani F, Ejaz A, Spolverato G, et al. Perioperative blood transfusion and the prognosis of pancreatic cancer surgery: systematic review and meta-analysis. Ann Surg Oncol. 2015;22:4382-4391.

[38]. Saleh A, Ihedioha U, Babu B, Evans J, Kang P. Is estimated intra-operative blood loss a reliable predictor of surgical outcomes in laparoscopic colorectal cancer surgery? Scott Med J.2016; 61:167-170.

[39]. Ito Y, Kanda M, Ito S, Mochizuki Y, Teramoto H, Ishigure K, et al. Intraoperative blood loss is associated with shortened postoperative survival of patients with stage II/III gastric cancer: analysis of a multi-institutional dataset. World J Surg.2019;43:870-877.

[40]. Arima K, Hashimoto D, Okabe H, Inoue R, Kaida T, Higashi T, et al. Intraoperative blood loss is not a predictor of prognosis for pancreatic cancer. Surg Today. 2016;46:792-797.

[41]. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B; Global Onco-Anesthesia Research Collaboration Group. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. Can J Anaesth. 2019;66:546-561.

[42]. Jiao B, Yang C, Huang NN, Yang N, Wei J, Xu H. Relationship between volatile anesthetics and tumor progression: unveiling the mystery. Curr Med Sci.2018;38:962-967.

[43]. Elias K, Kang S, Liu X, Horowitz NS, Berkowitz RS, Frendl G. Anesthetic selection and disease-free survival following optimal primary cytoreductive surgery for stage III epithelial ovarian cancer. Ann Surg Oncol. 2015;22:1341-1348.

[44]. Catalano F, Mengardo V, Trecca A, Tomezzoli A, Rodella L, Cerofolini A, et al. The impact of experience on short- and long-term outcomes on gastric ESD: a western series. Updates Surg. 2019;71:359-365.

Tables

Due to technical limitations, Tables 1 - 4 are only available for download from the Supplementary Files section.

Figures

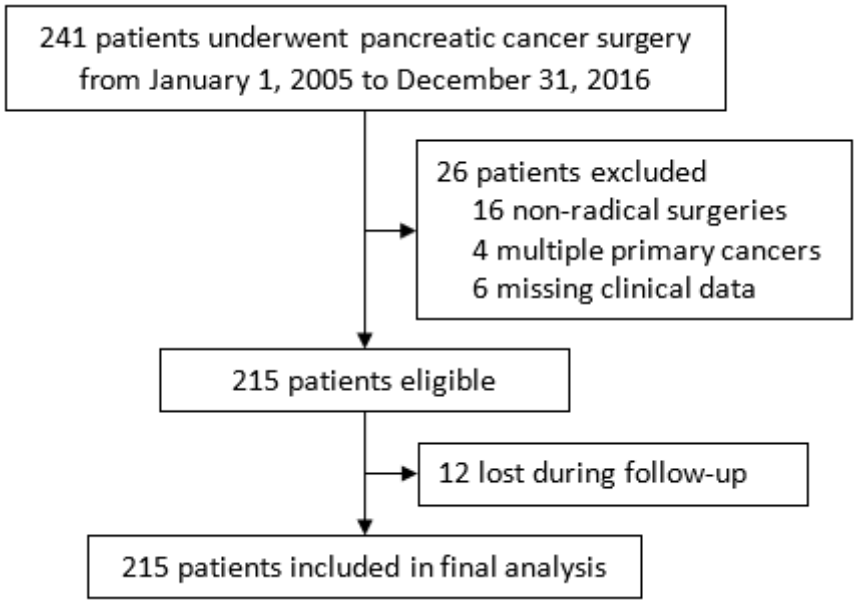

Figure 1

Flowchart of the study.

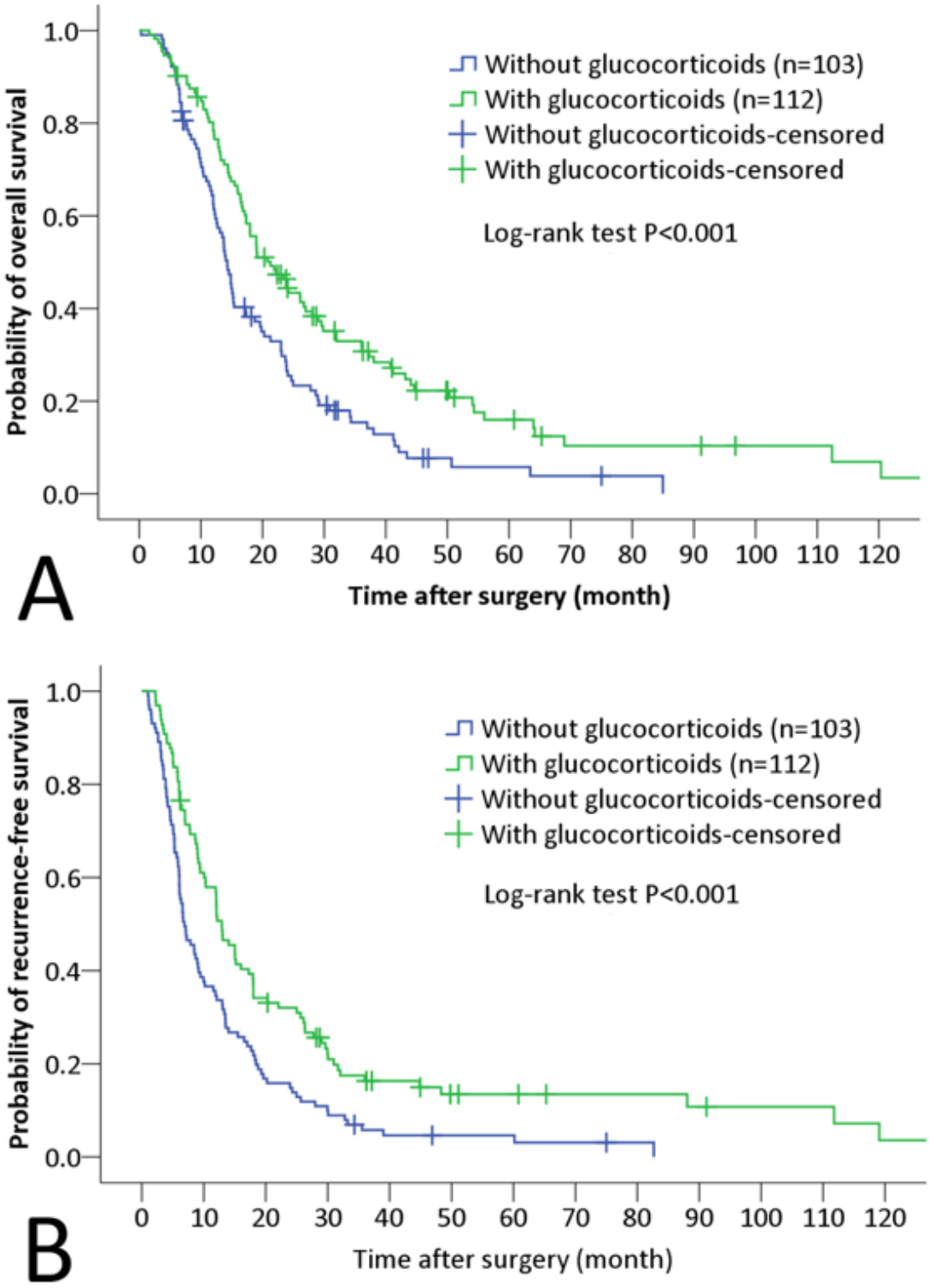

Figure 2

Survival curves of patients with or without perioperative glucocorticoids after pancreatic cancer surgery. (A) The overall survival was significantly longer in patients with glucocorticoids than in those without (Log-rank test P<0.001). (B) The recurrence-free survival was significantly longer in patients with glucocorticoids than in those without (Log-rank test P<0.001). +, subjects who were censored.

Supplementary Files

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- BMCSupplementalTable218490.docx
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