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ORIGINAL RESEARCH

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The effects of dexmedetomidine on postoperative tumor recurrence and patient survival after breast cancer surgery: a feasibility study

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Abstract

Purpose Dexmedetomidine (Dexmed) is a highly selective alpha 2 adrenoceptor (α_2-AR) agonist with excellent sedation and analgesic effects and is frequently used in breast cancer surgery. However, the exact impact of Dexmed on breast cancer prognosis is still unclear. The primary objective of this pilot study was to explore study feasibility (recruitment and dropout rates) for future large-scale randomized controlled trial (RCT) to test the hypothesis that intraoperative Dexmed reduced recurrence-free survival (RFS) and overall survival (OS) in patients after breast cancer surgery.

Methods Interviews with patients were performed during the anesthetic preoperative visit for informed consent. Adult females scheduled for a mastectomy due to primary breast cancer were 1:1 randomised to saline (Group Control) or Dexmed (Group Dexmed) treatment groups. The primary outcomes were descriptions of study feasibility (recruitment and dropout rates). We also performed a preliminary analysis of RFS (time from surgery to the earliest date of recurrence/metastasis) and OS (time from surgery to the date of all-cause death) and collected data on percentages/numbers of circulating immune cells at pre- and 24 h post-operation.

Results A total of 964 patients were screened; 40% (385/964) met the inclusion criteria, among which 39% (150/385) were enrolled and randomly assigned to either Group Control ($n=75$) or Group Dexmed ($n=75$). The median follow-up duration was 49 months (interquartile range (IQR): 34–58 months) for Group Control and 48 months (IQR: 33–60 months) for Group Dexmed. Five percent (5%, 8/150) patients were lost to follow-up and 1% (2/150) died. There was no significant difference in RFS and OS. The percentage/number of natural killer (NK), B and T-cell subsets and the $CD4^+/CD8^+$ ratio were similar between groups at 24 h post-operation.

Conclusion The pilot study was feasible to deliver. In a future definitive trial, the lower recruitment rate may be improved by increasing the number of anesthesiologists involved in the study. The study about the effects of Dexmed on long-term prognoses of breast cancer patients that is planned to follow this pilot study is a large-scaled

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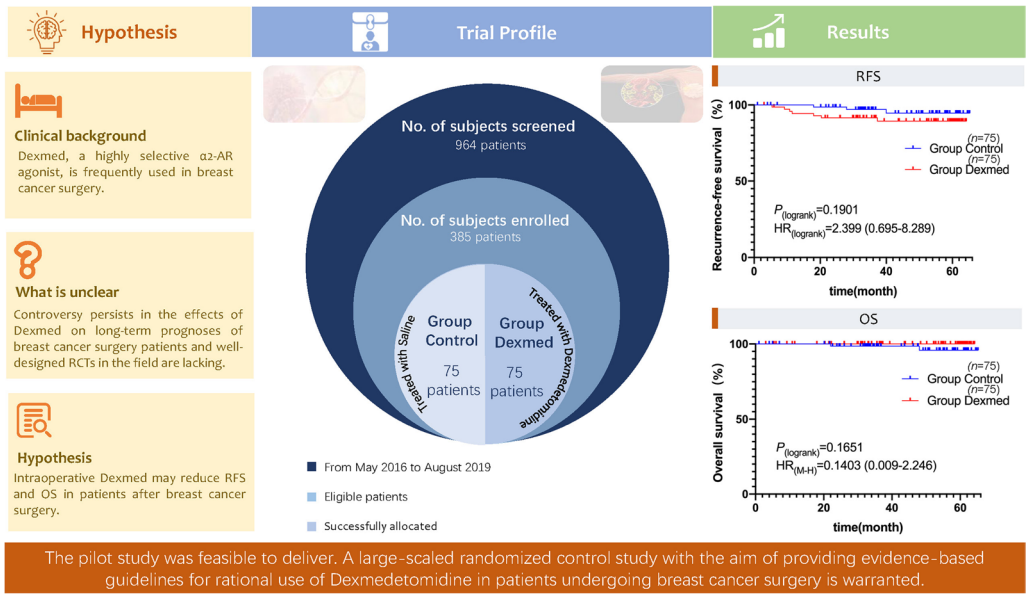
randomized control study with the aim of providing evidence-based guidelines for rational use of Dexmed in patients undergoing breast cancer surgery.

Trial registration Registered at ClinicalTrials.gov on October 20, 2016 (ID: NCT03109990).

Keywords Dexmedetomidine, Breast cancer, Recurrence-free survival, Overall survival

Graphical Abstract



1 Introduction

Breast cancer has become the most common malignancy in women [1]. According to the latest data from the database GLOBOCAN 2020, more than 2,250,000 new breast cancer cases were diagnosed annually. It also considered the second leading cause of cancer-related death in women, accounting for 15.5% of cancer-related deaths worldwide [2]. Surgery to remove the breast cancer is a usual treatment, and possibly combined with systemic therapy for some individuals [3].

While surgery remains the most effective treatment for breast cancer, surgical manipulation and perioperative events may exert negative impacts on long-term oncological outcomes in patients with breast cancer [4–6]. For example, it was reported back in the early 20th century that stress response and immunosuppression induced by surgery drove residual breast cancer cell proliferation, invasion and migration [7]. As an important component of perioperative events, anaesthesia may also profoundly affect cancer outcomes. Specifically, it was proposed that inhalational volatiles and opioids could stimulate cancer progression and impair survival [8, 9], whereas propofol and local anaesthetics may have potential anticancer properties [9–11]. In line with these observations, Buggy et al. reported that the neutrophil-lymphocyte ratio, an inflammatory marker for poor prognosis in solid tumors and reduced time to disease recurrence [12, 13], was significantly lower in patients receiving propofol-paravertebral when compared with the inhalational agent-opioid anaesthesia in primary breast cancer surgery [14]. A recent prospective, randomised trial showed that neutrophil extracellular trapping, which is an immunological mechanism strongly linked to increased metastatic risk, was significantly decreased by perioperative intravenous lidocaine in women undergoing breast cancer resection [15].

Dexmedetomidine (Dexmed) is a highly selective alpha 2 adrenergic receptor (α_2-AR) agonist and is frequently used as an adjunct to anaesthesia during cancer surgery due to its excellent sedative and analgesic effects. Although Dexmed attenuates perioperative stress and inflammation [16–18], it may enhance mammary tumor growth by activating α_2-AR [19]. By activating α2-AR/ERK signaling pathway, Xia et al. showed that Dexmed upregulated proliferation, migration and invasion abilities of human breast cancer cells and

increased the weight of xenotransplant breast tumors [20]. Our previous study indicated that in patients undergoing surgery for primary breast cancer, perioperative Dexmed administration influenced the serum milieu which favoured MCF-7 cell malignancy [21]. However, whether perioperative Dexmed affected long-term breast cancer surgery patient prognoses remains unknown.

In this study, we conducted a prospective, randomised, controlled pilot trial to derive preliminary information on whether intravenous Dexmed administration during breast cancer surgery was associated with an enhanced local or metastatic recurrence and reduced overall survival (OS) in patients with breast cancer. As the immune system is critical for antitumor efficacy, we monitored key immune cells (natural killer (NK), B, $CD3^+$, $CD4^+$ and $CD8^+$ T cells) and the $CD4^+/CD8^+$ ratio (marker reflecting immune competence and associated with the prognosis of patients with tumors) [22] at pre- and 24 h post-operation in a subset of patients. Pilot trial data will be used to determine study feasibility (recruitment and dropout rates) and sample size calculations for future definitive studies.

2 Methods

2.1 Trial format and ethical considerations

This is a single-centre, prospective, randomised, double-blinded, placebo-controlled pilot clinical trial that was approved by the Clinical Research Ethics Committee of Renji Hospital (2016–037) and registered in the international database ClinicalTrial.gov (reg no: NCT03109990). Patients were recruited at Renji Hospital, which was affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China, following the Good Clinical Practice guidelines and the Declaration of Helsinki. Written and informed consent was obtained from patients or authorised surrogates before inclusion.

2.2 Subject selection

Inclusion criteria were as follows: (1) female patients aged 18–75 y, (2) diagnosed with primary breast cancer, (3) American Society of Anesthesiologists scores I–III and (4) scheduled for mastectomy. Patients were excluded if they had the following: (1) previous breast surgery; (2) diagnosed with inflammatory breast cancer; (3) addiction to opioids (impaired control over opioids use, compulsive use, or continued use despite harm, and craving [23]); (4) serious major mental or physical illnesses (heart, pulmonary, hepatic or renal diseases); (5) malignant tumors in other organs or (6) contradictions or an allergy to Dexmed.

2.3 Randomisation and blinding

Interviews with patients were performed during the anesthetic preoperative visit for informed consent. Sample randomisation sequences were generated in a 1:1 ratio using the PROC programme in SAS (version 9.2, SAS Institute Inc.) and sealed in identical opaque envelopes. Randomisation was stratified by menopausal status, which has been reported to influence the recurrence rates of breast cancer [24]. Envelopes were opened by nurses not involved in caring for study patients before the start of the intervention. Nurses prepared study medications according to group allocation. Therefore, patients and study personnel involved in patient care were blinded to treatments. The investigators following up the patients were also masked to their group allocation. Patients were randomly allocated in a 1:1 ratio to receive either intravenous Dexmed (Group Dexmed) or the same 0.9% saline volume (Group Control) during surgery.

2.4 Procedures

Patients in both groups had breast cancer surgery under general anaesthesia. A routine intravenous anaesthesia induction was performed as follows: 0.05 mg/kg midazolam, 1.0 mg/kg lidocaine, 1.0–2.0 mg/kg propofol, 0.15–0.2 mg/kg cisatracurium and 3–6 μg/kg fentanyl or 0.2–0.5 μg/kg sufentanil. Endotracheal intubation was performed 3 min after induction, and the mechanical ventilation parameters were as follows: fresh air flow (fraction of inspired oxygen 0.5) 2.0 L/min, tidal volume 6–8 mL/kg, respiratory rate 10–12 times/min to maintain the end-tidal carbon dioxide ($EtCO_2$) partial pressure 35–40 mmHg. Anaesthesia was maintained with total intravenous anaesthesia using 0.1–0.2 μg/(kg/min) remifentanil, 4–8 mg/(kg/h) propofol and cisatracurium when needed to maintain the bispectral index value ranging between 40–60.

Ephedrine or phenylephrine was used if the systolic blood pressure (SBP) was < 90 mmHg or dropped ≥ 30% from baseline for > 5 min. Atropine was used to correct bradycardia when the heart rate was slower than 50 beats per min. Intraoperative hypertension was managed by increasing the anaesthetic depth or administering urapidil or nicardipine.

Before surgery ended, all patients were given 1 μg/kg fentanyl or 0.1 μg/kg sufentanil to alleviate postoperative pain. No patient-controlled analgesia was postoperatively used. Supplemental analgesics were provided with non-steroidal anti-inflammatory drugs when the visual analogue scale (VAS) pain score was ≥ 4 in wards.

2.5 Intervention

Before anaesthesia, patients in Group Dexmed received intravenous Dexmed at 1 μg/kg, as an initial loading

dose within 15 min, followed by infusion maintenance of 0.5 μg/kg/h for 2 h during surgery. Thus, each patient received 2 μg/kg Dexmed in total (if the operation was < 2 h, the infusion was performed until the operation ended and the total Dexmed was recorded). Patients in Group Control received the same 0.9% saline volume.

2.6 Records and measurements

Baseline data included demographics, menopausal status, comorbidities, tumor characteristics, tumor-node-metastasis stages, pre-operative laboratory examinations (routine blood, blood coagulation functions and liver and renal function tests) and pre-operative neoadjuvant chemotherapy. The following intraoperative data were recorded: anaesthesia duration, surgery method, anaesthetic and other medication types and doses, bleeding volume, blood transfusion, fluid balance and urinary output. The daily pain intensity (by VAS scores at rest) within 3 days after surgery was also recorded.

To investigate the possible effects of Dexmed on the immune system, blood samples were collected and sent for lymphocyte analysis when staff in the Clinical Laboratory Department were available. Blood was collected before anaesthesia induction and at 24 h postoperatively to measure the numbers/percentages of NK, B, $CD3^+$, $CD4^+$ and $CD8^+$ T cells, and also the $CD4^+/CD8^+$ ratio.

The first follow-up was scheduled postoperatively at 2 weeks. Subsequently, patients were evaluated every 3 months during the first year, every 6 months during the second year and once a year thereafter. Investigators contacted patients by phone, and upon their return, doctors recorded whether postoperative anticancer treatments were administered and also the interval examination results. Local recurrence was defined as one or more tumors in the ipsilateral chest wall and lymphatic drainage areas of the operated side after primary tumor excision. Metastatic recurrence was defined as one or more tumors in distant tissues or organs, such as the contralateral breast, lung, bone, liver and supraclavicular lymph nodes. Systemic treatments after surgery included chemotherapy, hormonal therapy, targeted therapy and radiotherapy. Specific treatment plans for patients were decided by surgeons following the Chinese Society of Clinical Oncology Guidelines for the Diagnosis and Treatment of Breast Cancer.

The primary outcome was study feasibility (recruitment and dropout rates). We also performed a preliminary analysis of recurrence-free survival (time from surgery to the earliest date of recurrence/metastasis) and OS (time from surgery to the date of all-cause death) and collected data on the enumeration (percentages/numbers) of NK, B, $CD3^+$, $CD4^+$ and $CD8^+$ T cells, and the $CD4^+/CD8^+$ ratio at pre- and 24 h post-operation, to reflect changes in the immune system after surgery. Patients lost to follow-up were censored.

2.7 Statistical analysis

No power calculations were performed. The sample size of 150 patients was hypothesised as achievable in the 3–4 y follow-up to allow for a meaningful evaluation of intervention effects.

Normal distributions of numerical variables were tested using Kolmogorov-Smirnov tests or histograms to display data distributions. If $P > 0.05$ or histograms showed a classic bell curve, variables were considered normally distributed and were represented by the mean ± standard deviation. Otherwise, data were represented as the median (IQR). Variance homogeneity tests were also performed. Normally distributed variables with homogenous variance were compared with independent-sample *t*-tests. Mann-Whitney U tests were used to compare continuous variables not meeting these principles.

For categorical variables, showing with *n* (%), we used chi-square, continuity correction chi-square or Fisher exact tests for statistical analyses. If the *P*-value of baseline variables in groups were > 0.05, then the baseline variables were considered balanced.

Recurrence-free survival (RFS) and OS were compared between groups using Kaplan-Meier analyses and log-rank tests. Effect size was expressed as hazard ratios (HRs) and 95% confidence interval (CI). The number/percentage of lymphocytes and the $CD4^+/CD8^+$ ratio, were compared using a two-way analysis of variance followed by Bonferroni's multiple comparisons tests.

Statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

3 Results

Between May 2016 and August 2019, 964 patients were screened; 40% (385/964) met the inclusion criteria, among which 39% (150/385) were enrolled and randomly assigned to either Group Control ($n = 75$) or Group Dexmed ($n = 75$), as shown in Fig. 1. All patients strictly followed protocols and were included in intention-to-treat or per-protocol analyses. Five percent (5%, 8/150) patients were lost to follow-up and 1% (2/150) died during the follow-up. The median follow-up duration was 49 months (IQR: 34–58 months) in Group Control and 48 months (IQR: 33–60 months) in Group Dexmed. Follow-up ended on September 30th, 2021.

Baseline demographics and tumor information were generally comparable between groups (Table 1), except for patients with diabetes, which were slightly higher in Group Control; however, fasting plasma glucose levels were similar between groups.

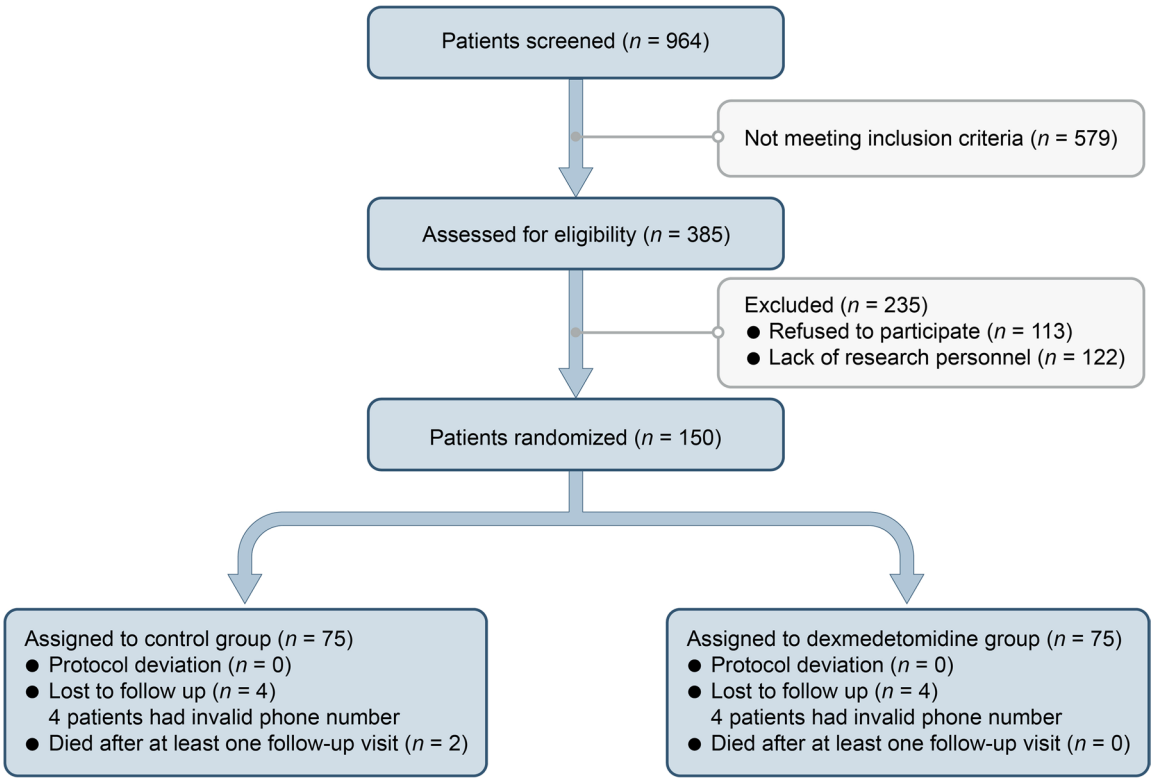


Fig. 1 Study flow diagram

Intraoperative and follow-up data were summarised (Table 2). As expected, patients in Group Dexmed received considerably more Dexmed than Group Control (Table 2). Interestingly, more patients in Group Dexmed were given antihypertensive drugs (including urapidil and nicardipine), whereas fewer were intraoperatively administered ephedrine to maintain SBP. Propofol consumption was also higher in Group Dexmed than in Group Control, although levels were not statistically significant. Most antihypertensive drugs were injected before or during anaesthesia induction, when patients were receiving the initial Dexmed loading dose, indicating the predominance of peripheral vasoconstriction effects of Dexmed when the plasma concentrations increased rapidly. Consistent with the bradycardia-inducing effects of Dexmed, more patients in Group Dexmed received atropine during anaesthesia maintenance. Intraoperative urine output was also significantly higher in Group Dexmed when compared with Group Control patients (Table 2), which is not surprising given the diuretic effects of Dexmed. Postoperative pain intensity was similar between groups.

When follow-up ended, neither RFS nor OS differed between the two groups, with seven events (9.3%) in Group Dexmed versus three (4.0%) in Group Control (HR, 2.399; 95% CI: 0.695–8.289; $P=0.1901$) in RFS analysis and 0 events in Group Dexmed versus two (2.67%) in Group Control (HR, 0.1403; 95% CI: 0.009–2.246; $P=0.1651$) for OS analysis (Fig. 2). Two deaths in Group Control were caused by multiple distant metastases. Interestingly, although the overall RFS did not differ between groups, RFS rate was consistently lower in Group Dexmed than Group Control in the follow-up four postoperative years (Table 3).

The enumeration of circulating immune cells, including percentage/number of NK, B, $CD3^+$T, $CD4^+$T and $CD8^+$T cells, and also the $CD4^+/CD8^+$ ratio, were not significantly different between groups at 24 h after surgery (Fig. 3 and Supplementary Table 1), indicating that Dexmed per se did not affect immune systems. Notably, $CD3^+$ and $CD4^+$ T-cell percentages/numbers were significantly lower postoperatively when compared with corresponding pre-surgical baseline levels, indicating that the surgery acutely suppressed the immune system (Fig. 1C, D and Supplementary Table 1).

4 Discussion

In this pilot study, we preliminarily investigated if Dexmed administration during surgery affected breast cancer prognoses. We screened 964 patients and finally included 150 for analysis. The total recurrence was 6.67%, which is consistent with a documented 5–10% recurrence survival [25]. We hypothesised that Dexmed usage during breast cancer

Table 1 Baseline data

	Group Control ($n=75$)	Group Dexmed ($n=75$)	*P* value
Age (yr), mean (SD)	56.27 (10.72)	56.05 (11.17)	0.91
Body-mass index (kg/m^2), mean (SD)	23.55 (3.18)	23.37 (3.26)	0.73
Menopause status, *n*/total *N* (%)			0.52
Premenopausal	22/75 (29%) [1]	26/75 (35%)	
Postmenopausal	52/75 (69%)	49/75 (65%)	
Comorbidity, *n*/total *N* (%)			
Hypertension	25/75 (33%)	21/75 (28%)	0.48
Diabetes	9/75 (12%)	2/75 (3%)	**0.03**
Stroke	2/75 (3%)	1/75 (1%)	1
Heart disease[a]	6/75 (8%)	2/75 (3%)	0.28
Lung disease[b]	2/75 (3%)	1/75 (1%)	1
Others[c]	1/75 (1%)	2/75 (3%)	1
ASA score, *n*/total *N* (%)			0.48
I	26/75 (35%)	22/75 (29%)	
II	49/75 (65%)	53/75 (71%)	
III	0/75	0/75	
Neoadjuvant chemotherapy, *n*/total *N* (%)	15/75 (20%)	20/75 (27%)	0.33
Laboratory tests			
WBC count (1×10^9/L), mean (SD)	6.88 (8.26) [3]	6.74 (2.69) [5]	0.88
Hemoglobin (g/L), mean (SD)	117.71 (25.28) [3]	121.79 (15.99) [5]	0.23
Platelets (1×10^9/L), mean (SD)	221.01 (57.79) [3]	223.04 (58.97) [5]	0.84
Albumin (g/L), mean (SD)	42.77 (3.26) [1]	42.22 (4.22) [2]	0.38
ALT (U/L), mean (SD)	19.18 (17.76) [1]	19.05 (10.88) [2]	0.95
AST (U/L), mean (SD)	19.64 (10.98) [1]	19.70 (7.59) [2]	0.97
BUN (mmol/L), mean (SD)	4.89 (1.59) [1]	4.65 (1.19) [3]	0.29
Cr (μmol/L), mean (SD)	61.68 (20.81) [1]	59.57 (10.13) [2]	0.44
FPG (mmol/L), mean (SD)	5.59 (1.36) [2]	5.39 (1.29) [3]	0.38
PT (s), mean (SD)	10.96 (1.45) [2]	11.12 (0.84) [2]	0.40
INR, mean (SD)	0.97 (0.02) [2]	1.10 (0.12) [2]	0.30
Maximum tumor diameter (cm), mean (SD)	2.18 (1.04) [9]	2.42 (0.96) [3]	0.15
Pathological type of breast cancer, *n*/total *N* (%)			0.22
Carcinoma in situ	6/75 (8%)	4/75 (5%)	
Invasion ductal carcinoma	65/75 (87%)	62/75 (83%)	
Invasion lobular carcinoma	0/75 (0)	4/75 (5%)	
Others	4/75 (5%)	5/75 (7%)	
IHC subtype, *n*/total *N* (%)[d]			0.82
Luminal A	12/75 (16%)	14/75 (19%)	
Luminal B	53/75 (71%)	47/75 (64%)	
Her-2 enriched	5/75 (7%)	6/75 (8%)	
Basal-like	5/75 (7%)	7/75 (9%)	

Table 1 (continued)

	Group Control ($n=75$)	Group Dexmed ($n=75$)	*P* value
Tumor-node-metastasis stage, *n*/total *N* (%)[e]			0.11
0[f]	1 (1%)	1 (1%)	
I	35 (47%)	24 (32%)	
II	26 (35%)	40 (53%)	
III	4 (5%)	6 (8%)	
IV	1 (1%)	0 (0)	
X	8 (11%)	4 (5%)	

Data are presented as the mean (standard deviation, SD) or *n* (%). Patients with missing data are marked in square brackets. Numeric variables were analysed using independent-sample *t* or Mann–Whitney U tests, and the categorical variables were analysed using chi-square, continuity correction chi-square or Fisher exact tests to ascertain a balanced baseline. $P > 0.05$ was considered balanced between Group Dexmed and Group Control

Dexmed Dexmedetomidine, *ASA* American Society of Anesthesiologists, *WBC* White blood cells, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *BUN* Blood urea nitrogen, *Cr* Creatinine, *FPG* Fasting plasma glucose, *INR* International Normalized Ratio, *PT* Prothrombin time

[a] Included coronary heart disease, arrhythmia, valvular disease and cardiomyopathy

[b] Included chronic bronchitis, emphysema, COPD, asthma, bronchiectasis and pulmonary tuberculosis

[c] Included hypothyroidism, depression and rheumatoid arthritis

[d] According to 2022 Chinese guidelines for the diagnosis and treatment of breast cancer from the National Health Commission of the People's Republic of China

[e] According to the American Joint Committee on Cancer (AJCC) 8th edition on tumor-node-metastasis (TNM) classification

[f] One case was diagnosed as in situ lobular carcinoma in the Group Control: it was considered a benign entity and was removed from TNM staging according to AJCC guidelines. It was assigned to TisN0M0 according to the 7th edition. We were unable to classify stages in 11 cases due to the following: (1) missing data or (2) irregular-shaped cancer foci

surgery could promote tumor recurrence and metastasis, which was suggested by our previous in vitro study [21]. In the current study, our data suggested that Dexmed administration during breast cancer surgery neither affected RFS and OS in patients nor patient immunity levels. However, during the initial 4 years following surgery, which coincides with the peak period for breast cancer recurrence [26], intraoperative Dexmed treatment seemed to associate with a reduced RFS. Ours is the first prospective randomised trial to report survival outcomes in this field and has a potential clinical impact. However, as our sample size was small, further large sample size, multicenter, double-blinded randomised control trials (RCTs) are warranted.

In recent years, the potential for Dexmed to affect tumor progression has attracted much attention. For example, a propensity score-matched retrospective study by Cata et al. found that in non-small cell lung cancer, intraoperative Dexmed was significantly associated with a worsened OS [27]. However, controversy still persists. A meta-analysis evaluating the impact of Dexmed administration on the survival of children and adolescents with multiple cancers revealed that Dexmed, used intraoperatively and/or early postoperatively, was not associated with survival [28]. Another 3-year follow-up study on older patients undergoing major noncardiac surgery, primarily for cancer, demonstrated that intraoperative Dexmed did not have an association with OS, but it did improve recurrence-free and event-free survival [29]. Moreover, a recent publication in *Nature* revealed that various α2-receptor agonists can exert anti-tumor effects by triggering tumor immune rejection and tumor regression in multiple models [30]. In breast cancer, although clinical data is lacking, animal studies are extensive, with most indicating possible detrimental effects of Dexmed on cancer outcomes. Bruzzone et al. reported that a 0.05 mg/kg daily Dexmed injection possibly enhanced tumor growth in mice with medroxyprogesterone acetate-induced breast cancer [31]. Elsewhere, researchers demonstrated that a single injection of clinically relevant Dexmed doses (5–20 μg/kg/h for 2 h) enhanced distal tumor metastasis in rats receiving intravenous mammary adenocarcinoma MADB106 cells [19]. Therefore, prospective clinical studies are urgently required to ascertain if a causal relationship exists between perioperative Dexmed use and oncological outcomes in patients with breast cancer.

To address this, we conducted a prospective, randomised, double-blinded trial to provide information for future studies. Patients strictly followed protocols and the most important prognostic factors were well balanced between both trial arms. Both recurrence and survival rates were generally comparable to previous studies [32, 33]. Neither of the primary outcomes, RFS and OS, were significantly different between groups, suggesting that Dexmed had no apparent influence on increasing breast cancer recurrence, in contrast with in vitro and animal studies. However, it is noteworthy that 1-, 2-, 3- and 4-year RFS rates were consistently lower in Group Dexmed when compared with Group Control. Although overall rates did not differ between groups,

Table 2 Intraoperative and follow-up data

	Group Control (*n* = 75)	Group Dexmed (*n* = 75)	*P* value
Duration of anesthesia (min), mean (SD)	172 (144, 205)	192 (154, 221)	0.08
Duration of surgery (min), mean (SD)	153.12(40.61)	164.76(56.89)	0.15
Type of resection, *n*/total *N* (%)			0.56
Simple mastectomy	40/75 (53%)	33/75 (44%)	
Modified radical operation of mastocarcinoma	35/75 (47%)	42/75 (56%)	
Lymph node dissection, *n*/total *N* (%)			0.40
Sentinel only	0/75 (0)	2/75 (3%)	
Axilla	40/75 (53%)	35/75 (47%)	
None/missing	35/75 (47%)	38/75 (51%)	
Intraoperative medication			
Dexmedetomidine (ug), mean (SD)	0	118.77 (16.11)	**< 0.001**
Midazolam (mg), mean (SD)	2.94 (0.42)	2.89 (0.43)	0.48
Fentanyl (mg), mean (SD)	0.23 (0.05)	0.22 (0.04)	0.36
Sufentanil (ug), mean (SD)	20.10 (1.01)	20.59 (2.42)	0.35
Remifentanil (mg), mean (SD)	1.41 (0.58)	1.15 (0.69)	0.21
Total morphine equivalent (mg), mean (SD)[a]	163.21 (60.52)	176.35 (69.63)	0.22
Cisatracurium (mg), mean (SD)	27.07 (6.82)	29.29 (7.26)	0.06
Propofol (mg), mean (SD)	1145.41 (327.11)	1211.89 (456.25)	0.31
Lidocaine (mg), mean (SD)	57.41 (10.76)	58.0 (11.13)	0.74
Use of ephedrine, *n*/total *N* (%)	28/75 (37%)	10/75 (13%)	**0.001**
Use of norepinephrine, *n*/total *N* (%)	2/75 (3%)	1/75 (1%)	1
Use of atropine, *n*/total *N* (%)	10/75 (13%)	14/75 (18%)	0.50
Use of antihypertensive drugs, *n*/total *N* (%)[b]	10 (13%)	23 (31%)	**0.01**
Crystalloid fluid (ml), median (IQR)	500 (500, 1000)	500 (500, 800)	0.59
Colloid fluid (ml), median (IQR)	500 (300, 500)	500 (300, 500)	0.46
Estimated bleeding volume (ml), median (IQR)	50 (20, 50)	50 (20, 50)	0.52
Blood transfusion volume (ml), median (IQR)	0 (0)	0 (0)	/
Urine output (ml), median (IQR)	300 (200, 462.5) [1]	800 (500, 1000)	**< 0.001**
24 h VAS score at rest, *n*/total *N* (%)			1
< 4	73/75 (97%)	73/75 (97%)	
4 ~ 7	2/75 (3%)	1/75 (1%)	
> 7	0 (0)	1/75 (1%)	
48 h VAS score at rest, *n*/total *N* (%)			1
< 4	73/75 (97%)	73/75 (97%)	
4 ~ 7	2/75 (3%)	2/75 (3%)	
> 7	0/75 (0)	0/75 (0)	
72 h VAS score at rest, *n*/total *N* (%)			1
< 4	75/75 (100%)	75/75 (100%)	
4 ~ 7	0/75 (0)	0/75 (0)	
> 7	0/75 (0)	0/75 (0)	
Postoperative anticancer therapy, *n*/total *N* (%)			0.74
Chemotherapy	52/75 (69%)	52/75 (69%)	
Radiotherapy	11/75 (15%)	15/75 (20%)	
Molecular targeting therapy	16/75 (21%)	15/75 (20%)	

Data are presented as the mean (standard deviation), median (interquartile range) or *n* (%). Patients with missing data are listed in square brackets. $P < 0.05$ (bold) was considered unbalanced between groups

VAS Visual Analogue Scale

[a] Calculated intravenous morphine equivalent, including all opioids used intraoperatively: 10 mg morphine (intravenous [iv]) = 0.1 mg fentanyl (iv) = 10 μg sufentanil (iv) = 100 μg remifentanil (iv)

[b] Antihypertensive drugs used intraoperatively included urapidil and nicardipine

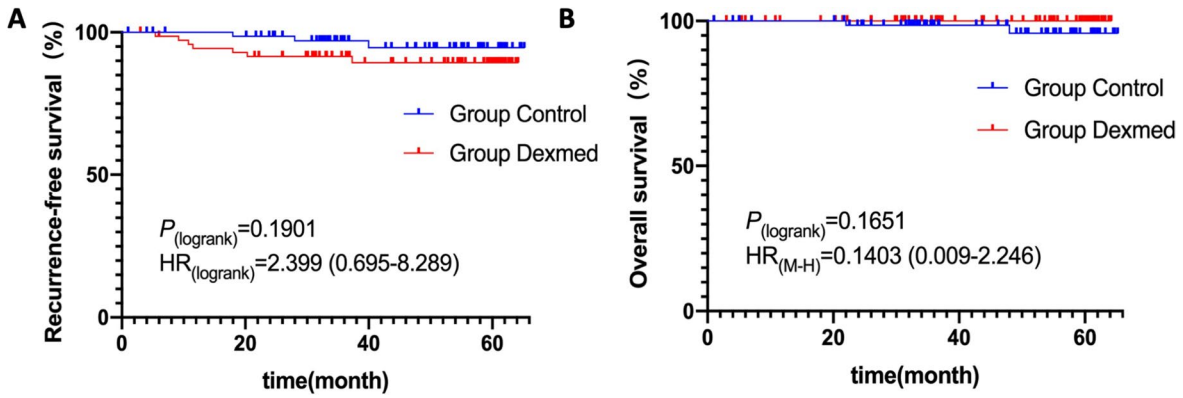


Fig. 2 Kaplan–Meier estimates of recurrence-free survival (**A**) and overall survival (OS) (**B**). Kaplan-Meier analyses were performed using log-rank tests. Effect size was expressed as the hazard ratio (HR) and 95% confidence interval (CI). M-H: Mantel-Haenszel. The OS effect size was expressed as HR using the M-H test as opposed to the log-rank test. Points on lines indicate patients lost to follow-up

Table 3 The RFS rates of patients in Group Control and Group Dexmed

Time	Group Control				Group Dexmed			
	RFS rates (95% CI)	No. events	No. censored	No. left	RFS rates (95% CI)	No. events	No. censored	No. left
	1			75	1			75
1 year	1	0	4	71	0.94(0.89–0.99)	4	4	67
2 years	0.98(0.96–1)	1	8	66	0.92(0.85–0.98)	6	6	63
3 years	0.97(0.93–1)	2	28	45	0.92(0.85–0.98)	6	22	47
4 years	0.95(0.88–1)	3	37	35	0.89(0.82–0.97)	7	32	36

RFS Recurrence-free survival, *CI* Confidence interval

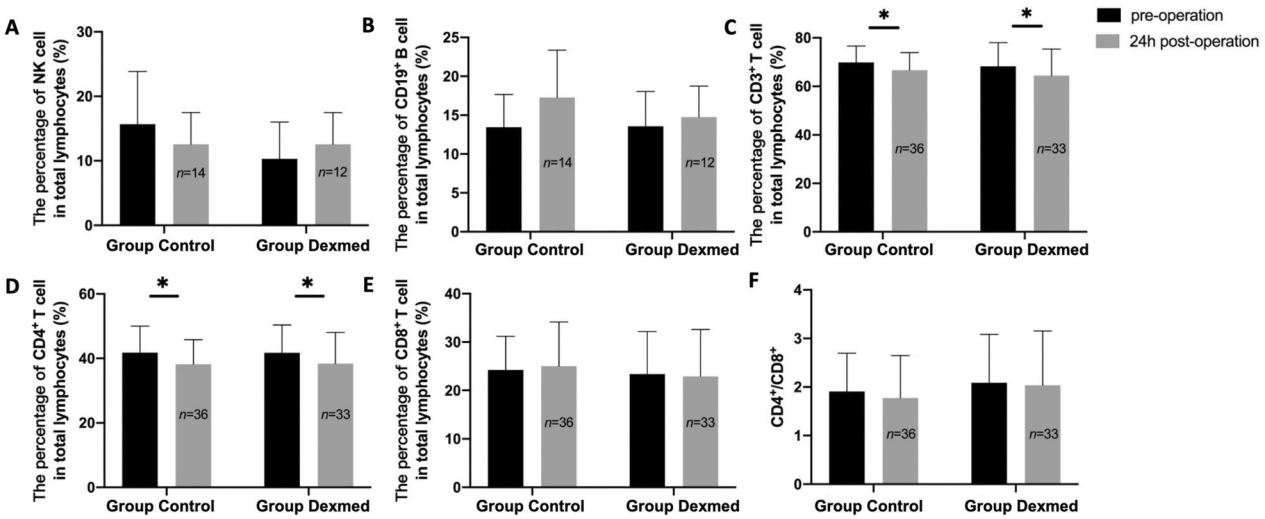


Fig. 3 The percentages of natural killer (NK), B and T-cell subsets at pre-operation and 24 h post-operation in groups. In total lymphocytes, the percentage of **A** NK, **B** $CD19^+$ B, **C** $CD3^+$ T, **D** $CD4^+$ T and **E** $CD8^+$ T cells in groups at pre-operation and 24 h post-operation periods. **F** The $CD4^+$ /$CD8^+$ T cell ratio in groups at indicated time points. $n = 14–36$ in Group Control. $n = 12–33$ in Group Dexmed. Dexmed: dexmedetomidine. Values were expressed as the mean ± standard deviation. Multiple comparisons were performed using a two-way analysis of variance followed by Bonferroni's multiple comparisons test. *$P < 0.05$ compared with pre-operative numbers in the same group

considering the small patient population who met the 3-year or longer-term follow-up, it is possible that the differences in RFS between groups in the later years could become statistically significant if patient numbers were increased. Therefore, large-scale, multicenter trials based on our findings are warranted.

The underlying Dexmed mechanism and its possible effect on cancer outcomes have mainly focused on the immune system, which has key role in breast cancer progression and treatment responses [34, 35]. Inada et al. reported that Dexmed inhibited antitumor immunity in mice with thymoma, possibly by reducing interleukin-12 (IL-12) levels produced by antigen-presenting cells, and decreasing cytotoxic T-cell activity [36]. Several studies also suggested that Dexmed inhibited the migration and antigen processing/presentation functions of dendritic cells (DCs) from mouse bone marrow [37, 38]. Apart from immunity, Dexmed may also affect tumor progression via other mechanisms: a recent study revealed that Dexmed upregulated the expression and secretion of transmembrane protease serine 2, a key metastasis driver expressed in various cancer cells, by activating α2-AR/STAT3 signalling in MCF-7 and MDA-MB-231 breast cancer cell lines [39]. These data were consistent with an earlier study that reported tumor collagen structures in breast tumor slices from Dexmed-treated mice were altered and drove the tumor cell proliferation, local invasion and metastasis [40].

Based on the literature, we tested a secondary hypothesis that Dexmed affected different lymphocyte populations. Using 7–36 patient samples, our negative findings provided certain information for the field, but our data were caveated by being underpowered. Nonetheless, considerable T-cell inhibition caused by surgery was detected by this power, indicating that even Dexmed has certain influence on lymphocyte numbers, the influence is mild. Another possibility was that lymphocytes are part of the adaptive immunity, whereas Dexmed may have mainly affected the innate immunity, as reported by different studies [37, 38, 41]. Since innate immunity (i.e., DCs, macrophages and neutrophils) is also critical for breast cancer development, future studies investigating the effects of Dexmed on changes in innate immune cell populations in patients with breast cancer are also needed.

In conclusion, this pilot study was feasible to deliver. We identified no differences in RFS or OS rates between patients with breast cancer who did or did not receive Dexmed treatment during surgery. However, we observed a trend toward a worse RFS rate in patients receiving Dexmed in the first 4 y after surgery, which may have some clinical significance. Owing to our small sample size, a large-scale RCT is required. The findings of this feasibility study support the conduct of our planned confirmatory RCT that is designed to provide a definitive answer to whether Dexmed treatment reduces RFS and OS of patients undergoing breast cancer surgery.

Abbreviations

α_2-AR	Alpha 2 adrenoceptor
CI	Confidence interval
DCs	Dendritic cells
Dexmed	Dexmedetomidine
HR	Hazard ratio
IQR	Interquartile range
NK	Natural killer
OS	Overall survival
RCT	Randomized controlled trial
RFS	Recurrence-free survival
SBP	Systolic blood pressure
VAS	Visual analogue scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44254-023-00037-z.

Additional file 1: Supplementary Table 1. Comparison of the absolute number of T cells, NK cells and B cells at pre- and 24h post-operation between the two groups.

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Authors' contributions

Jiamei Luo: Data collection and curation, formal analysis, original draft, drafting and editing. Wei Xuan and Jiaxin Sun: Investigation and data curation. Xiaoqiang Wang, Yumiao Shi and Yiqi Zhang: Data curation. Wenjin Yin: Investigation and methodology. Huigang Shu: Conceptualization and funding acquisition. Jinsong Lu: Conceptualization and investigation. Jie Tian: Conceptualization, funding acquisition, methodology, review and editing.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study has been approved by the Clinical Research Ethics Committee of Renji Hospital (2016–037) Patients were recruited at Renji Hospital, which was affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China, following the Good Clinical Practice guidelines and the Declaration of Helsinki. Written and informed consent was obtained from patients or authorized surrogates before inclusion.

Consent for publication
All authors gave their consent for publication.

Competing interests
The authors declare no competing interests.

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References

1. Perera SK, Jacob S, Wilson BE, Ferlay J, Bray F, Sullivan R, et al. Global demand for cancer surgery and an estimate of the optimal surgical and anaesthesia workforce between 2018 and 2040: a population-based modelling study. Lancet Oncol. 2021;22(2):182–9.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
3. Waks AG, Winer EP. Breast cancer treatment. JAMA. 2019;321(3):288–300.
4. Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes: a narrative review. Br J Anaesth. 2019;123(2):135–50.
5. Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. 2014;3(4):900–8.
6. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol. 2018;15(4):205–18.
7. Baum M, Demicheli R, Hrushesky W, Retsky M. Does surgery unfavourably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases? Eur J Cancer. 2005;41(4):508–15.
8. Nguyen J, Luk K, Vang D, Soto W, Vincent L, Robiner S, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. Br J Anaesth. 2014;113 Suppl 1:i4–13.
9. Zhang J, Chang C-L, Lu C-Y, Chen H-M, Wu S-Y. Paravertebral block in regional anesthesia with propofol sedation reduces locoregional recurrence in patients with breast cancer receiving breast conservative surgery compared with volatile inhalational without propofol in general anesthesia. Biomed Pharmacother. 2021;142:111991.
10. D'Agostino G, Saporito A, Cecchinato V, Silvestri Y, Borgeat A, Anselmi L, et al. Lidocaine inhibits cytoskeletal remodelling and human breast cancer cell migration. Br J Anaesth. 2018;121(4):962–8.
11. Johnson MZ, Crowley PD, Foley AG, Xue C, Connolly C, Gallagher HC, et al. Effect of perioperative lidocaine on metastasis after sevoflurane or ketamine-xylazine anaesthesia for breast tumour resection in a murine model. Br J Anaesth. 2018;121(1):76–85.
12. Orditura M, Galizia G, Diana A, Saccone C, Cobellis L, Ventriglia J, et al. Neutrophil to lymphocyte ratio (NLR) for prediction of distant metastasis-free survival (DMFS) in early breast cancer: a propensity score-matched analysis. ESMO Open. 2016;1(2):e000038.
13. Forget P, Bentin C, Machiels JP, Berliere M, Coulie PG, De Kock M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. Br J Anaesth. 2014;113 Suppl 1:i82–7.
14. Ní Eochagáin A, Burns D, Riedel B, Sessler DI, Buggy DJ. The effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and return to intended oncological therapy. Anaesthesia. 2018;73(5):603–11.
15. Galoș EV, Tat TF, Popa R, Efrimescu CI, Finnerty D, Buggy DJ, et al. Neutrophil extracellular trapping and angiogenesis biomarkers after intravenous or inhalation anaesthesia with or without intravenous lidocaine for breast cancer surgery: a prospective, randomised trial. Br J Anaesth. 2020;125(5):712–21.
16. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. Br J Anaesth. 2019;123(6):777–94.
17. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Crit Care Med. 2004;32(6):1322–6.
18. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. J Anesth. 2008;22(3):221–8.
19. Lavon H, Matzner P, Benbenishty A, Sorski L, Rossene E, Haldar R, et al. Dexmedetomidine promotes metastasis in rodent models of breast, lung, and colon cancers. Br J Anaesth. 2018;120(1):188–96.
20. Xia M, Ji NN, Duan ML, Tong JH, Xu JG, Zhang YM, et al. Dexmedetomidine regulate the malignancy of breast cancer cells by activating α2-adrenoceptor/ERK signaling pathway. Eur Rev Med Pharmacol Sci. 2016;20(16):3500–6.
21. Liu Y, Sun J, Wu T, Lu X, Du Y, Duan H, et al. Effects of serum from breast cancer surgery patients receiving perioperative dexmedetomidine on breast cancer cell malignancy: a prospective randomized controlled trial. Cancer Med. 2019;8(18):7603–12.
22. Hernberg M, Muhonen T, Pyrhönen S. Can the CD4+/CD8+ ratio predict the outcome of interferon-alpha therapy for renal cell carcinoma? Ann Oncol. 1997;8(1):71–7.
23. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569–76.
24. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015;386(10001):1353–61.
25. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288–300.
26. Qu F-L, Mao R, Liu Z-B, Lin C-J, Cao AY, Wu J, et al. Spatiotemporal patterns of loco-regional recurrence after breast-conserving surgery. Front Oncol. 2021;11:690658.
27. Cata JP, Singh V, Lee BM, Villarreal J, Mehran JR, Yu J, et al. Intraoperative use of dexmedetomidine is associated with decreased overall survival after lung cancer surgery. J Anaesthesiol Clin Pharmacol. 2017;33(3):317–23.
28. Owusu-Agyemang P, Cata JP, Kapoor R, Zavala AM, Williams UU, Van Meter A, et al. An analysis of the survival impact of dexmedetomidine in children undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Int J Hyperthermia. 2018;35(1):435–40.
29. Xing M-W, Li C-J, Guo C, Wang B-J, Mu D-L, Wang D-X. Effect of intraoperative dexmedetomidine on long-term survival in older patients after major noncardiac surgery: 3-year follow-up of a randomized trial. J Clin Anesth. 2023;86:111068.
30. Zhu J, Naulaerts S, Boudhan L, Martin M, Gatto L, Van den Eynde BJ. Tumour immune rejection triggered by activation of α2-adrenergic receptors. Nature. 2023;618(7965):607–15.
31. Bruzzone A, Piñero CP, Castillo LF, Sarappa MG, Rojas P, Lanari C, et al. Alpha2-adrenoceptor action on cell proliferation and mammary tumour growth in mice. Br J Pharmacol. 2008;155(4):494–504.
32. Fernandez-Martinez A, Krop IE, Hillman DW, Polley M-Y, Parker JS, Huebner L, et al. Survival, pathologic response, and genomics in CALGB 40601 (Alliance), a neoadjuvant phase III trial of paclitaxel-trastuzumab with or without lapatinib in HER2-positive breast cancer. J Clin Oncol. 2020;38(35):4184–93.
33. Lynch SP, Lei X, Chavez-MacGregor M, Hsu L, Meric-Bernstam F, Buchholz TA, et al. Multifocality and multicentricity in breast cancer and survival outcomes. Ann Oncol. 2012;23(12):3063–9.
34. Andre F, Dieci MV, Dubsky P, Sotiriou C, Curigliano G, Denkert C, et al. Molecular pathways: involvement of immune pathways in the therapeutic response and outcome in breast cancer. Clin Cancer Res. 2013;19(1):28–33.

35. Linares-Galiana I, Berenguer-Frances MA, Cañas-Cortés R, Pujol-Canadell M, Comas-Antón S, Martínez E, et al. Changes in peripheral immune cells after intraoperative radiation therapy in low-risk breast cancer. J Radiat Res. 2021;62(1):110–8.
36. Inada T, Shirane A, Hamano N, Yamada M, Kambara T, Shingu K. Effect of subhypnotic doses of dexmedetomidine on antitumor immunity in mice. Immunopharmacol Immunotoxicol. 2005;27(3):357–69.
37. Ueshima H, Inada T, Shingu K. Suppression of phagosome proteolysis and Matrigel migration with the α2-adrenergic receptor agonist dexmedetomidine in murine dendritic cells. Immunopharmacol Immunotoxicol. 2013;35(5):558–66.
38. Chen G, Le Y, Zhou L, Gong L, Li X, Li Y, et al. Dexmedetomidine inhibits maturation and function of human cord blood-derived dendritic cells by interfering with synthesis and secretion of IL-12 and IL-23. PLoS One. 2016;11(4):e0153288.
39. Chi M, Shi X, Huo X, Wu X, Zhang P, Wang G. Dexmedetomidine promotes breast cancer cell migration through Rab11-mediated secretion of exosomal TMPRSS2. Ann Transl Med. 2020;8(8):531.
40. Szpunar MJ, Burke KA, Dawes RP, Brown EB, Madden KS. The antidepressant desipramine and α2-adrenergic receptor activation promote breast tumor progression in association with altered collagen structure. Cancer Prev Res (Phila). 2013;6(12):1262–72.
41. Su X, Fan Y, Yang L, Huang J, Qiao F, Fang Y, et al. Dexmedetomidine expands monocytic myeloid-derived suppressor cells and promotes tumour metastasis after lung cancer surgery. J Transl Med. 2018;16:347.

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