


The Role of Dexmedetomidine in Tumor-Progressive Factors in the Perioperative Period and Cancer Recurrence: A Narrative Review

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Abstract: Dexmedetomidine, a specific α_2 adrenergic receptor agonist, is highly frequently used in the perioperatively for its favorable pharmacology, such as mitigating postoperative cognitive dysfunction. Increasing attention has been recently focused on the effect of whether dexmedetomidine influences cancer recurrence, which urges the discussion of the role of dexmedetomidine in tumor-progressive factors. The pharmacologic characteristics of dexmedetomidine, the tumor-progressive factors in the perioperative period, and the relationships between dexmedetomidine and tumor-progressive factors were described in this review. Available evidence suggests that dexmedetomidine could reduce the degree of immune function suppression, such as keeping the number of CD3+ cells, NK cells, CD4+/CD8+ ratio, and Th1/Th2 ratio stable and decreasing the level of proinflammatory cytokine (interleukin 6 and tumor necrosis factor-alpha) during cancer operations. However, dexmedetomidine exhibits different roles in cell biological behavior depending on cancer cell types. The conclusions on whether dexmedetomidine would influence cancer recurrence could not be currently drawn for the lack of strong clinical evidence. Therefore, this is still a new area that needs further exploration.

Keywords: dexmedetomidine, cancer recurrence, surgery, immune, inflammation

Introduction

The leading cause of mortality currently in patients <85 years is cancer, which adds a tremendous economic and medical burden worldwide.¹ Surgery under anesthesia remains the first choice for cancer patients and plays a crucial role in cancer diagnosis, stage confirmation, and reconstruction. Metastatic recurrence is still reasonably frequent although surgical resection should be curative in local tumor lesions. An increasing number of studies have recently indicated that anesthetic drugs, as one of the essential perioperative components, may be involved in cancer recurrence by influencing the factors of tumor progression,² such as propofol and locoregional anesthesia leading less immunosuppression,³ opioids stimulating cytological behavior of several tumor cells.⁴ Dexmedetomidine is a frequently increasingly used anaesthetic in the department of anesthesiology and intensive care unit (ICU) for its favorable pharmacology of suitable sedation, pain alleviation, and reduced odds of postoperative cognitive dysfunction.⁵ However, there still lacks of reviews on the theme of whether it plays a role in cancer recurrence as the amount of related researches grows sharply. Some studies

showed that dexmedetomidine could protect immunity function, reduce inflammation reaction in patients who underwent cancer surgeries, and inhibit tumor cell growth, which may be favorable for outcomes of cancer patients.^{6–8} However, some studies claimed dexmedetomidine decreased overall survival after lung cancer surgery⁹ and stimulated the growth of some kinds of cancer cells.^{10,11} Hence, this review makes a comprehensive description, exploring the role of dexmedetomidine in tumor-progressive factors in the perioperative period that may affect cancer recurrence.

Methods

Two authors (QC and MLG) comprehensively searched PUBMED, EMBASE, and SCOPUS using the terms ((Dexmedetomidine or DEX or Dexmedetomide) and (Tumor or Tumour or Oncology or Cancer or Neoplasm)) from inception to July 2021 to gather fundamental and clinical studies exploring the relationship between dexmedetomidine and cancer. Moreover, references related to this topic were also searched. Clinical Registration Websites (<https://clinicaltrials.gov/> and <http://www.chictr.org.cn>) were searched for ongoing clinical trials observing whether dexmedetomidine is associated with cancer recurrence.

Chemistry and Clinical Pharmacology of Dexmedetomidine

Dexmedetomidine is a usual anesthetic agent approved in the United States by the Food and Drug Administration in 1999 for the sedation of critical patients in the ICU. Furthermore, the applied range of dexmedetomidine in the clinical setting expanded to patients being operated on in 2008.¹² The chemical structure of dexmedetomidine is 5-[(1S)-1-(2,3-dimethyl phenyl) ethyl]-1H-imidazole with molecular formula C₁₃H₁₆N₂ (Figure 1).¹² As a particular agonist to α_2 adrenergic receptor, the selectivity ratio of α_2 adrenoceptor to α_1 adrenoceptor is 1600:1, which was more potent than clonidine with a selectivity ratio of 200:1.⁵ The protein binding of dexmedetomidine was 94%, and the half-life distribution was approximately 6 min with a clearance half-life of approximately 2–3 h. Dexmedetomidine could be metabolized by direct glycosylation and cytochrome P450 enzymes. Moreover, 95% and 4% of its metabolites are excreted in the urine and feces, respectively, and are not affected by fat mass.¹³ The α_2 adrenergic receptors were distributed in the brain and other peripheral organs (eg, the spine, spleen, kidney, aorta, lung, skeletal muscle, heart, and liver; Table 1). Dexmedetomidine exerts diverse pharmacologic actions by specific binding to α_2 adrenergic receptors in different tissues and cells. The most remarkable feature of dexmedetomidine is that patients remain easily rousable under dexmedetomidine-based sedation,¹⁴ which is primarily mediated by the activation of pre- and postsynaptic α_2 adrenergic receptors in locus coeruleus¹⁵ where the brain is responsible for mediating wakefulness and sleep. Furthermore, multiple studies showed that dexmedetomidine-based sedation could reduce the risk of postoperative delirium in surgery patients, especially in the elderly.^{16–19} The analgesic effect of dexmedetomidine is mediated by activating α_2 adrenergic receptors in locus coeruleus and the spine²⁰ through interneuron hyperpolarization and reduction of neurotransmitter release (eg, substance P and glutamate).¹² In addition, dexmedetomidine exerts a protective role in ischemia–reperfusion injury in cerebral,²¹ spinal cord,²² kidney,²³ lung,²⁴ heart,²⁵ liver,²⁶ and intestine,²⁷ which has promising application and benefit for patients.

Direct and Indirect Tumor-Progressive Factors in the Perioperative Period

The perioperative period is a critical time because the physiological status of patients dramatically changes. The equilibrium between the immune system and neoplasm growth was considered steady before surgery trauma.²⁸

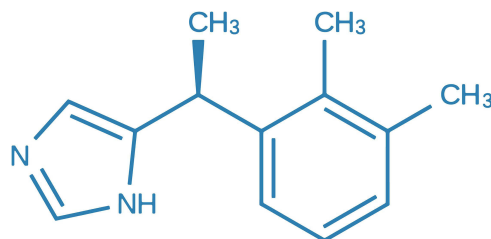


Figure 1 The chemical structure of dexmedetomidine.

Table 1 Classification of α_2 Adrenergic Receptors

Receptor Type	The Primary Signal Transduction Mechanism	The distribution in Human Tissue	Physiological Functions	Therapeutic Drugs (Indications)
α_2A	Gi/Go (adenylate cyclase inhibition, potassium channel, calcium channel, and phospholipase A2 stimulation)	Brain > spleen > kidney > aorta = lung = skeletal muscle > heart = liver	Presynaptic inhibition of noradrenaline release, hypotension, sedation, analgesia, and hypothermia	Agonists: Dexmedetomidine, medetomidine, romifidine, clonidine, brimonidine, detomidine, lofexidine, xylazine, tizanidine, guanfacine, and amitraz (antihypertensives, sedatives and treatment of opiate dependence, and alcohol withdrawal symptoms)
α_2B	Gi/Go (adenylate cyclase inhibition, potassium channel, calcium channel)	Kidney \gg liver > brain = lung = heart = skeletal muscle (also reported in aorta and spleen)	Vasoconstriction	Antagonists: phentolamine, yohimbine, idazoxan, atipamezole, trazodone, mianserin, and mirtazapine (aphrodisiac and antidepressants, and reversal of α_2 -AR agonist-induced sedation)
α_2C	Gi/Go (adenylate cyclase inhibition, potassium channel, calcium channel)	Brain = kidney (also reported in spleen, aorta, heart, liver, lung, skeletal muscle)	Presynaptic inhibition of noradrenaline release	

Abbreviation: α_2 -AR, α_2 adrenergic receptor.

Surgery alters the interplay of neuroendocrine, inflammatory, immune, and metabolic pathways of patients,²⁹ which initiates a cascade of stress responses by activating the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) axis.³⁰ SNS and HPA axis activation is closely related to immune dysfunction.³¹ Adrenoreceptors are also distributed on lymphoid organs and immune cells³² that could be activated by catecholamines and glucocorticoids secreted from adrenal glands, leading to an imbalance between Th1 and Th2 cells, shifting in favor of the Th2 cells, decreasing NK cell cytotoxicity, resulting in immune function suppression.^{33,34}

Circulating tumor cells (CTCs), which are the cause of distant metastases,³⁵ are shed from the solid tumor into the blood in many cancer patients, which are also significantly increased intraoperatively during tumor resection, especially in open approach than minimally invasive surgery, in the central vein than peripheral venous blood.^{36,37} Moreover, the detection rate of CTCs is much higher during surgical manipulation, particularly in cancer with lymphatic invasion.³⁸

Moreover, tissue injury, stress, and infection caused by surgery trauma could lead to the inflammatory response involved in the coordinated delivery of blood components to the site of infection and injury.³⁹ Tissue-resident macrophages and mast cells will recognize the initial signal subsequently, leading to the production of various inflammatory mediators, including chemokines, cytokines, vasoactive amines, eicosanoids, and products of proteolytic cascades and inducing neutrophils to move to the position of the inflammation.⁴⁰ However, the inflammatory process persists and acquires new characteristics if the acute inflammatory response fails to eliminate the pathogen. Thus, it would transform into the persistent inflammation state involving the formation of granulomas and tertiary lymphoid tissues,⁴¹ providing favorite sites by disrupting endothelial surfaces and liberating growth factors for the seedings from CTCs released by surgery manipulation,^{42,43} which was called *inflammatory oncotaxis*.⁴⁴ Moreover, neutrophil extracellular traps (NETs), relative to the inflammatory reaction induced by surgical trauma,⁴⁵ could attract cancer cells to form distant metastases.⁴⁶

Hence, the depressed immunologic function, the inflammation state, may be indirect tumor-progressive factors aroused by surgery stress or injury, which acted as *helpers* in cancer recurrence. Moreover, the CTCs and distant microscopic metastases could be the direct tumor-progressive factors, whose vitality is essential to cancer recurrence. The form of distant metastases facilitated by tumor-progressive factors by surgery stress or injury in the perioperative period is presented below (Figure 2).

The Role of Dexmedetomidine in Indirect Tumor-Progressive Factors (Immunologic Function and Inflammation State) During Cancer Operations

Dexmedetomidine is widely used to maintain anesthesia in operations,¹⁷ including cancer surgeries.^{7,47} Moreover, dexmedetomidine infusion may influence the immunologic function and inflammation state of cancer patients. Sixty-two patients

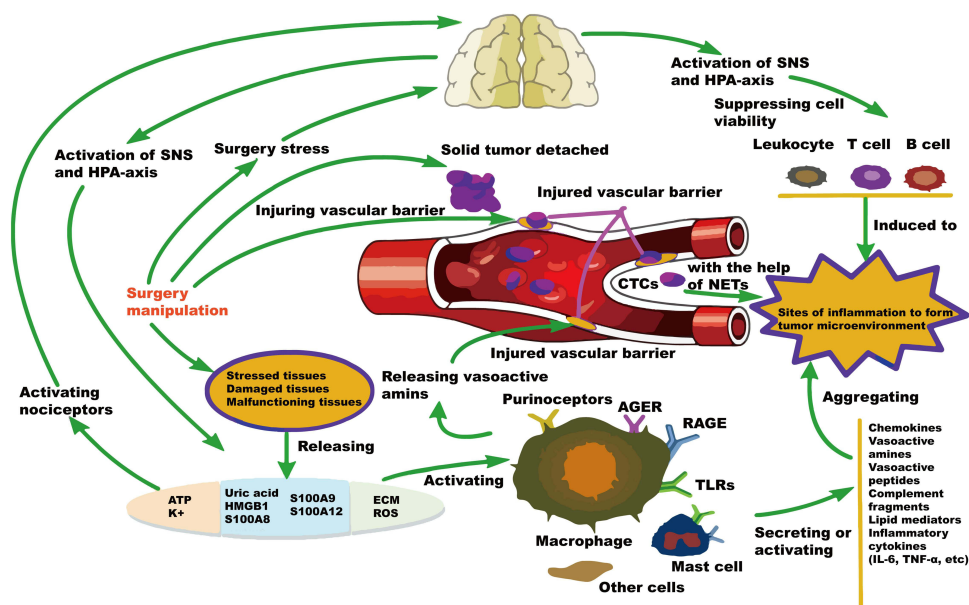


Figure 2 The distant metastases form facilitated by tumor-progressive factors by surgery stress. On the one hand, surgery can promote the shedding of cells from solid tumors to form circulating cancer cells. On the other hand, it could activate the HPA axis and SNS to suppress the immune system, which helps tumor cells escape immune surveillance, and localize to target organs (eg, with the help of the NETs and clusters of neutrophils). Moreover, the released inflammatory mediator by immune and mast cells incited by damage signals or activated HPA axis and SNS will lead to vascular barrier injury and inflammation, which tends to form the tumor microenvironment if the status exists persistently.

Abbreviations: SNS, sympathetic nervous system; HPA axis, hypothalamic–pituitary–adrenal axis; HMGB1, high-mobility group box 1 protein; S100A8, S100A9, and S100A12, members of the S100 calcium-binding protein family; ECM, components of the extracellular matrix; ROS, reactive oxygen species; CTCs, circulating tumor cells; NETs, neutrophil extracellular traps; AGER and RAGE, for advanced glycation end-product-specific receptor; TLRs, Toll-like receptors.

undergoing radical mastectomy were pumped with 1 µg/kg dexmedetomidine for 10 min before anesthesia induction showed increased CD4+ and NK cell levels compared with the control.⁷ This high level was maintained for 48 h and only returned to normal in about 72 h. Patients pumped with 1 µg/kg dexmedetomidine intravenously at 0.2 µg/kg·h during radical gastric cancer resection showed elevated CD3+ and CD4+ levels and CD4+/CD8+ ratio and reduced interleukin (IL-6) and tumor necrosis factor-α (TNF-α) levels compared with the control.⁴⁷ Dexmedetomidine could also maintain Th1/Th2 balance and decrease IL-6 and TNF-α levels in patients undergoing radical gastrectomy.^{48,49} Patients pumped intravenously with 1 µg/kg dexmedetomidine for 10 min as a loading dose and maintained at 0.3 µg/(kg·h) until the end of hepatectomy had reduced IL-6 and TNF-α levels compared with the control.²⁷ Patients pumped with 1 µg/kg dexmedetomidine intravenously for 10–15 min as a loading dose and maintained at 1 µg/(kg·h) before colon cancer operation showed increased CD3+ and CD4+ levels, CD4+/CD8+ ratio, and Th1/Th2 ratio compared with the control.⁵⁰ Furthermore, Guo et al found that 1 µg/kg dexmedetomidine pumped intravenously for 10 min as a loading dose and maintained at 0.4 µg/(kg·h) until 30 min before the end of lung cancer operation reduced the TNF-α level of patients,⁵¹ which was also reported by other studies with different dexmedetomidine infusion rates.⁵² Moreover, dexmedetomidine infusion could also promote CD3+ and CD4+ levels and CD4+/CD8+ ratio and decrease IL-6 levels in lung cancer operation^{6,53–56} compared with the control. Patients pumped with 0.5 µg/kg dexmedetomidine intravenously for 15 min as a loading dose and maintained at 0.4 µg/(kg·h) until the end of oral cancer operation had elevated CD3+ and CD4+ levels and CD4+/CD8+ ratio.⁵⁷ In addition, patients pumped with 1 µg/kg dexmedetomidine intravenously for 15 min and maintained at 0.5 µg/(kg·h) until brain cancer operation ended had elevated CD3+ and CD4+ levels, CD4+/CD8+ ratio, and NK cell numbers.⁵⁸ In patients pumped with 0.3 µg/(kg·h) dexmedetomidine intravenously until the end of esophagus cancer operation had significantly decreased IL-6 levels compared with the control.⁵⁹ Other studies also demonstrated that intravenous infusion of dexmedetomidine could decrease IL-6 and TNF-α levels in esophagus cancer operation.⁶⁰ Moreover, dexmedetomidine infusion could decrease IL-6 and TNF-α levels in colorectum operation^{61,62} (the studies involved are listed in Table 2, and the details of the changes are shown in Supplementary Table 1).

Table 2 Studies Investigating the Effect of Dexmedetomidine on Immune Cells and Inflammatory Cytokines in Patients Undergoing Cancer Surgery

Author	Year	Number of Patients (Group D/C)	Physical Status of Patients	Cancer Surgery	Treatment in Group D	Treatment in Group C	CD3+	CD4+	CD4 +/CD8+	Th1/Th2	NK	IL-6	TNF- α
Wang et al ²⁷	2014	44 (22/22)	ASA II–III	Liver	1 μ g/kg DEX pumped intravenously for 10 min as a loading dose and maintained at 0.3 μ g/(kg h) until the end of the surgery	0.9% sodium chloride pumped similarly						↓	↓
Yang et al ⁷	2017	124 (62/62)	ASA II	Breast	1 μ g/kg DEX pumped intravenously for 10 min	0.9% sodium chloride pumped similarly	↑	↑	↑		↑	↓	
Wang et al ⁵⁰	2017	141 (72/69)	ASA I–II	Colon	1 μ g/kg DEX pumped intravenously for 10–15 min as a loading dose and maintained at 1 μ g/(kg h) before operation	0.9% sodium chloride pumped similarly	↑	↑	↑	↑		↓	
Wang et al ⁴⁸	2014	40 (20/20)	ASA I–II	Stomach	0.5 μ g/kg DEX pumped intravenously for 10 min as a loading dose and maintained at 1 μ g/(kg h) until 30 min before closing the peritoneum	0.9% sodium chloride pumped similarly				↑		↓	↓
Gao et al ⁵²	2015	50 (25/25)	ASA I–II	Lung	1 μ g/kg DEX pumped intravenously before induction of general anesthesia for 20 min	None							↓
Dong et al ⁴⁷	2017	74 (37/37)	ASA I–III	Stomach	1 μ g/kg DEX pumped intravenously at a velocity of 0.2 μ g/kg h during operation	0.9% sodium chloride pumped similarly	↑	↑	↑			↓	↓
Guo et al ⁵¹	2017	124 (62/62)	ASA I–II	Lung	1 μ g/kg DEX pumped intravenously for 10 min as a loading dose and maintained at 0.4 μ g/(kg h) until 30 min before the end of the operation	None							↓
Guo et al ⁷¹	2015	149 (76/73)	ASA I–III	Oral	DEX pumped intravenously at 0.2 μ g/kg/h for 12 h after the operation	0.9% sodium chloride pumped similarly						↓	

(Continued)

Table 2 (Continued).

Author	Year	Number of Patients (Group D/C)	Physical Status of Patients	Cancer Surgery	Treatment in Group D	Treatment in Group C	CD3+	CD4+	CD4 +/CD8+	Th1/Th2	NK	IL-6	TNF- α
Wen et al ⁵³	2020	54 (26/28)	ASA I-II	Lung	1 μ g/kg DEX pumped intravenously for over 10 min as a loading dose and maintained at 0.4 μ g/(kg h) until 30 min before the end of the operation	0.9% sodium chloride pumped similarly	↑	↑	↑			↓	↓
Wu et al ⁵⁸	2015	40 (20/20)	ASA I-II	Brain	1 μ g/kg DEX pumped intravenously for 15 min and maintained at 0.5 μ g/(kg h) until the end of the operation	0.9% sodium chloride pumped similarly	↑	↑	↑		↑		
Liu et al ⁵⁴	2020	120 (60/60)	ASA II-III	Lung	0.5 μ g/kg DEX pumped intravenously for 10 min and maintained at 0.5 μ g/(kg h) until 30 min before the end of the operation	0.9% sodium chloride pumped similarly						↓	↓
Kong et al ⁶	2018	120 (60/60)	ASA I-II	Lung	1 μ g/kg DEX pumped intravenously for 15 min and maintained at 0.5 μ g/(kg h) until 20 min before the end of the operation	0.9% sodium chloride pumped similarly	↑	↑	↑		↑	↓	↓
Gong et al ⁵⁹	2020	40 (20/20)	ASA II-III	Esophagus	DEX pumped intravenously for 0.3 μ g/(kg h) until the end of operation	0.9% sodium chloride pumped similarly						↓	
Tang et al ⁶⁰	2020	60 (27/26)	ASA I-III	Esophagus	0.6 μ g/kg DEX pumped intravenously for 15 min as a loading dose and maintained at 0.4 μ g/(kg h) until the end of the operation. After the operation, the patients were administered with PCA containing 1 μ g/mL of sufentanil plus 2.5 μ g/mL DEX	0.6 μ g/kg DEX pumped intravenously for 15 min as a loading dose and maintained at 0.4 μ g/(kg h) until the end of the operation. After the operation, the patients were administered with PCA containing 1 μ g/mL of sufentanil without DEX						↓	↓

Huang et al ⁵⁷	2021	64 (32/32)	ASA I-II	Oral	0.5 µg/kg DEX pumped intravenously in 15 min as a loading dose and maintained in 0.4 µg/(kg h) until the end of the operation	0.9% sodium chloride pumped similarly	↑	↑	↑				
Zhang et al ⁶¹	2019	140 (80/60)	ASA II-III	Colorectum	1 µg/kg DEX pumped intravenously for 15 min and maintained at 0.2–0.7 µg/(kg h) until 30 min before the end of the operation	0.9% sodium chloride pumped similarly						↓	
Xie et al ⁵⁵	2020	116 (58/58)	ASA II-III	Lung	1 µg/kg DEX pumped intravenously for 10 min and maintained at 0.3 µg/(kg h) until 20 min before the end of the operation	0.9% sodium chloride pumped similarly						↓	↓
Yi et al ⁶²	2018	246 (126/120)	ASA II-III	Colorectum	0.5 µg/kg DEX pumped intravenously for 15 min and maintained at 0.5 µg/(kg h) until the end of the operation	0.9% sodium chloride drip at a rate of 0.5 µg/kg/h.							↓
Yin et al ⁵⁶	2021	90 (48/42)	Not mentioned	Lung	0.5 µg/kg DEX pumped intravenously for 10 min and maintained at 0.5 µg/(kg h) until the end of the operation	None							↓

Notes: ↑ indicates patients treated with dexmedetomidine compared with the patients treated with saline where the levels of immune cells or inflammatory cytokines in the blood of patients significantly increased postoperatively; ↓ indicates patients treated with dexmedetomidine compared with patients treated with saline where the levels of immune cells or inflammatory cytokines in the blood of patients decreased significantly postoperatively.

These studies suggested that dexmedetomidine could regulate immunologic function and decrease the proinflammatory cytokine release in the perioperative period of cancer operations. The leading mechanism is that SNS and HPA activity stimulated by surgery stress could induce a redistribution of immune cells (eg, neutrophils, monocytes, and T cells) by secretion of catecholamines and cortisol.⁶³ Catecholamines induce the T and NK cells to move from the marginated pool (eg, bone marrow and lymph nodes) to the bloodstream temporarily.⁶⁴ Consequently, the T cells and monocytes were induced out of the bloodstream to the surgical site or the marginated pool. Thus, the number of NK and T cells decreased postoperatively.⁶⁵ However, α_2 adrenergic receptors are highly expressed in the pineal gland;⁶⁶ dexmedetomidine could reduce the adrenocorticotropic (ACTH) secretion and cortisol levels by binding to it.⁶³

IL-6 and TNF- α are mainly secreted from monocytes and macrophages. The inhibiting effect of dexmedetomidine on TNF- α and IL-6 secretions depend on two possible mechanisms. First, the attenuation of surgery stress by ACTH and cortisol reduction via dexmedetomidine could indirectly reduce the inflammation reaction given the close relationship between stress and inflammation.⁶⁷ Second, dexmedetomidine could directly influence monocytes and macrophages. Li et al reported that dexmedetomidine could attenuate NF κ B-p65 phosphorylation to decrease TNF- α production from LPS-stimulated murine BV-2 microglial cells and RAW264.7 macrophage cells.⁶⁸ A similar study also proved that dexmedetomidine could reduce TNF- α and IL-6 levels and enhanced IL-10 secretion from bone marrow-derived macrophages.²⁶

The current study shows that dexmedetomidine infusion could mediate the immunologic function and inflammation state of cancer patients. Similarly, a meta-analysis including 4842 patients suffering from different diseases showed that dexmedetomidine infusion significantly inhibited the release of epinephrine, norepinephrine, and cortisol,³⁰ leading to (1) increased number of NK cells; (2) increased ratio of CD4+/CD8+ and Th1/Th2 cells; and (3) decreased TNF- α and IL-6 levels. Moreover, a study from Shin et al⁶⁹ demonstrated that BALB/c nude mice with tumor pumped with Dexmedetomidine exhibited faster NK cell activity recovery and lower cortisol levels and TNF- α levels at 4 weeks after surgery when compared with the control that BALB/c nude mice with tumor pumped with the saline. The underlying mechanisms accounting for the phenomenon might be dexmedetomidine relieves the stress responses by regulating the sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) axis reaction, which were highly correlated to the equilibrium of immunity function and the inflammatory state, as presented in the introduction. As an evidence, Li et al⁷⁰ established a unique (lipopolysaccharide) LPS-induced acute lung injury (ALI) rate model with the bilateral cervical vagus nerve cut off (vagotomy), they found that dexmedetomidine could reduce LPS-induced IL-1 β , TNF- α , and catecholamine but increased acetylcholine in blood serum in the rate without vagotomy, but partially abolished by vagotomy, which suggested dexmedetomidine could play the role by high vagal nerve tone and α_2 -adrenoceptor activation.

Although Clinical trials have shown the effects of dexmedetomidine on immunomodulatory and anti-inflammatory. There are still several limitations. Firstly, the number of studies is relatively small, which requires multicenter studies with large samples to confirm the conclusion further. Secondly, long-term role of dexmedetomidine regulating immune function and inflammation in cancer patients, such as 5 year survival period, has not been investigated. Therefore, this is still a new area worthy of further research.

The Role of Dexmedetomidine in Direct Tumor-Progressive Factors (Proliferation, Migration, and Invasion of Cancer Cells)

Dexmedetomidine and Lung Cancer Cell

The latest fundamental study¹¹ from Wang et al found that dexmedetomidine could promote human lung cancer cell A549 proliferation and migration at the <0.001 nM level, which was far less than the blood concentration used in clinical settings. A549 cell quantity could be increased 1.2- and 1.7-folds at the 0.001- and 10-nM levels, respectively, and enhance cell migration by 2.2-fold vs vehicle at the 1-nM level. Moreover, Ki67 is one kind of nucleoprotein engaged in ribosomal RNA transcription.⁷² As one of the cell proliferation markers, it is expressed in the G1, S, G2, and M phases of the cell cycle, but not in the silent G0 stage. Ki67 expression was 2.9-fold over the control when the A549 cell was treated with 1 nM dexmedetomidine, meaning the A549 cell was in the active growth period.

Dexmedetomidine and Breast Cancer Cell

Some articles^{73,74} recently indicated that dexmedetomidine could promote the growth of human breast cancer cells. Xia et al found that dexmedetomidine could promote proliferation, migration, and invasion of human MDA-MB-231 breast cancer cells via the activation of $\alpha 2$ -adrenoceptor/ERK1/2 signaling.⁷³ The ERK1/2 signaling pathway is one of the classical pathways involved in many essential cell functions and regulates tumor cell progression.⁷⁵ The protein level of the phosphorylated ERK, $\alpha 2$ adrenoceptor increased when the MDA-MB-231 cell was treated with different dexmedetomidine levels ($>0.1 \mu\text{M}$) for 48 h.⁷³ This promotion role confirmed in vivo that the volumes and weight of the tumor in dexmedetomidine-treated mice were more massive than in the control group. Similarly, the migration capacity of cells was significantly improved when human MCF-7 and MDA-MB-231 cancer cells were treated with dexmedetomidine ($1 \mu\text{M}$) for 16 h.⁷⁶

Prolactin and relevant receptors (PrIR) had been found in several breast cancer cells,⁷⁷ and the role of PrIR stimulating breast cell proliferation⁷⁸ and the association of cancer risk and PrIR level before diagnosis <10 years had been confirmed.⁷⁹ Moreover, PrIR levels were an independent prognostic marker for breast cancer.⁸⁰ An interesting study by Castillo⁷⁴ revealed that the prolactin secretions of human T47D and MCF-7 breast cancer cells were promoted by dexmedetomidine at the 1-nM level and could be reversed by rauwolscine, an $\alpha 2$ adrenergic antagonist. The increasing PrIR could cause rapid STAT5 and ERK1/2 phosphorylation in MCF-7 and T47D cells and activate relevant cancer pathways.

Another study⁸¹ found that dexmedetomidine could alter the collagen structure of 4T1 mice breast cancer cells to promote growth. Second-harmonic generation (SHG) is a particular optical signal generated when laser contacts with nonlinear materials are more sensitive to microstructure change than the best fluorescence signal.⁸² Fibrillar collagen with detectable SHG signal was confirmed to promote tumor cell locomotion in breast tumor models^{83,84} and was associated with tumor cell proliferation, invasion, and metastasis.⁸⁵ The researchers treated the tumor mice with dexmedetomidine at a concentration of 10 or 25 mg/kg for 19 days and showed the increased tumor growth rate and the notable change in the number of SHG image pixels in the tumor removed from mice treated with dexmedetomidine.⁸¹

Moreover, [3H]thymidine is a raw material of compounding DNA, which has a radioactive character that could be detected to assess the reactivity of cells to drugs to promote proliferation. However, dexmedetomidine could enhance the incorporation rate of [3H]thymidine into the cell and enhance mouse breast tumor volume of C4-HD at a follow-up of 25 days of the experimental period without losing sensitivity to the $\alpha 2$ adrenoceptor after continuous treatment.⁸⁶ Also, another study from the same team showed that the stromal fibroblasts from breast tumors could also express $\alpha 2$ adrenergic receptors, and dexmedetomidine could promote fibroblast proliferation. Furthermore, the effect of proliferation could be reversed by $\alpha 2$ adrenergic antagonist, rauwolscine.⁸⁷

Dexmedetomidine and Colon Cancer Cell

Lavon et al explored the role of dexmedetomidine in the progression of mouse CT26 colon adenocarcinoma cells. They found that dexmedetomidine administered at the hypnotic dose of 3 or 12.5 $\mu\text{g}\cdot\text{kg}^{-1} \text{h}^{-1}$ could promote CT26 tumor metastasis numbers in the livers of female mice with CT26 tumor cells injected into the spleen 3 weeks previously.¹⁰

Dexmedetomidine and Ovarian Cancer Cell

Cai et al⁸ [6] found that dexmedetomidine could inhibit the growth rate of the NUTU-19 rat ovarian cancer cell by inhibiting the p38MAPK/NF- κB signaling pathway. The researchers injected NUTU-19 ovarian carcinoma cells into the right armpit of rats to form a solid tumor, then distributed the rats into different groups treated by different doses of dexmedetomidine or saline. Moreover, they set the rat group without tumors planted as the healthy group. However, the rats with the tumors in the dexmedetomidine group displayed more energy and better appetite than the saline group but not the healthy group. The same situation was presented when measuring the weight of the tumor. When comparing the pathological changes of ovarian cancer tissues from the saline group, the ovarian cancer tissues from the dexmedetomidine groups exhibited shrinkage of tumor cell and chromatin migration and patchy necrosis at different degrees. The p38 MAPK-dependent NF- κB signaling pathway is seen as playing the primary role in chemoresistance and cell damage and

having a crucial influence on the proliferation of malignant tumor cells, including ovarian cancer cells.⁸⁸ Moreover, Cai et al⁸ [6] discovered that the dexmedetomidine group presented significantly fewer expression signals of that pathway than the saline group.

Dexmedetomidine and Osteosarcoma Cell

A study by Wang et al⁸⁹ cultivated the human osteosarcoma cell MG63 combined with dexmedetomidine at different doses and found that 100 ng/mL of dexmedetomidine could significantly suppress cell viability after 12 h of treatment. Furthermore, 100 ng/mL of dexmedetomidine could significantly decrease the number of migrated MG63 cells and elevate the percentage of apoptotic MG63 cells after 24 h of treatment. MiR-520-3p is one of the noncoding RNAs that could suppress various human cancers.^{90–92} Moreover, AKT/mTOR pathway is essential in the disease process, especially in tumor progression,^{93,94} and could regulate human osteosarcoma cell proliferation and apoptosis.⁹⁵ They⁸⁹ found that miR-520-3p induced by dexmedetomidine could specifically bind to the 3'-UTR of AKT1 to inhibit MG63 osteosarcoma cell.

In summary, dexmedetomidine could directly promote proliferation, migration, and metastasis in some cancer cells (eg, lung, breast, and colon cancer cells) and restrain some ovarian cancer cells and osteosarcoma cancer cells by different mechanisms (Table 3).

Future Perspectives

Accumulating clinical studies have shown that dexmedetomidine is inclined to protect immunologic function and reduce inflammatory cytokine in the perioperative period of cancer surgeries, which may inhibit cancer recurrence factors. However, a few fundamental studies indicate that dexmedetomidine could facilitate the vitality of some human cancer cell lines (eg, MDA-MB-231, MCF-7, T47D, 4T1, and A549), which originate from breast or lung tissue. Thus, this arouses the interesting question: could the clinical application of dexmedetomidine be deleterious to the survival of cancer patients or accelerative to cancer recurrence? However, a lack of robust clinical evidence (ie, RCTs or meta-analysis of high-quality) exists on this theme. A study from MD Anderson Cancer Center⁹ investigating the relationship

Table 3 The Mechanism of the Role of Dexmedetomidine in Cell Biological Behaviors

Author	Year	Sources of Tumor	The Strain of Tumor Cell	Species	Mechanism of the Role of Dexmedetomidine on Cell Biological Behavior
Wang et al ¹¹	2018	Lung	A549	Human	High expression of cyclin A, D, E, and Ki67
Xia et al ⁷³	2016	Breast	MDA-MB-231	Human	High expression of phosphorylated ERK
Gargiulo et al ⁷⁶	2014	Breast	MCF-7	Human	Not mentioned
Castillo et al ⁷⁴	2017	Breast	T47D and MCF-7	Human	High expression of prolactin, STAT5, and phosphorylated ERK
Szpunar et al ⁸¹	2013	Breast	4T1	Human	Fibrillar collagen with upregulated detectable SHG signal
Bruzzzone et al ⁸⁶	2008	Breast	MC4-L5	Mouse	Absorption of upregulated [3H]thymidine
Chi et al ⁹⁶	2020	Breast	MDA-MB-231 and MCF-7	Human	Activation of α 2-adrenergic receptor/STAT3 signaling and promotion of TMPRSS2 secretion in exosomes through Rab11
Lavon et al ¹⁰	2018	Colon	CT26	Mouse	Not mentioned
Zheng et al ⁹⁷	2019	Ovarian	SKOV3	Human	Downregulation of HIF-1 α via miR-155
Cai et al ⁸	2017	Ovarian	NUTU-19	Rat	Downregulation of p38MAPK/NF- κ B signaling
Wang et al ⁸⁹	2018	Osteosarcoma	MG63	Human	Downregulation of AKT/mTOR pathway via miR-520-3p

between the intraoperative use of dexmedetomidine and lung cancer recurrence presented a decreased overall survival in patients using dexmedetomidine. However, the author reminded us of the significant limitation that dexmedetomidine may be used in patients with more severe comorbidities that were not captured in the database. Dexmedetomidine could improve the outcomes of critical patients (eg, heart disease patients). Perioperative dexmedetomidine used decreases the postoperative mortality of patients who underwent heart surgeries and decreased the delirium rate.^{98,99}

Moreover, some essential variables (eg, consumption of opioids or intraoperative volatile anesthetics) were not included in the final analysis, which was considered as potential factors influencing cancer recurrence.^{100,101} In addition, no difference in recurrence-free survival time with or without dexmedetomidine was noted. Another retrospective study from the same research group indicated that dexmedetomidine administration could not influence the survival of children and adolescents who had undergone major oncologic surgery.¹⁰²

Hence, it is still common to apply dexmedetomidine to cancer patients for its excellent pharmacological effect at this stage, especially in reducing postoperative delirium. Nevertheless, exploring the effect of the administration of dexmedetomidine on outcomes of cancer patients is still meaningful. A certain number of prospective randomized controlled trials are currently ongoing (NCT03109990: Impact of Dexmedetomidine on Breast Cancer Recurrence After Surgery; NCT03012971: Dexmedetomidine Supplemented Analgesia and Long-term Survival After Cancer Surgery; NCT04111926: Intraoperative Dexmedetomidine and long-term outcomes in the elderly after major surgery), aiming to assess whether dexmedetomidine would influence cancer recurrence and long-term survival in different cancer operations. Thus, this will bring more specific information to clinicians.

Conclusion

Dexmedetomidine could protect immunologic function, reduce inflammatory cytokine in the perioperative period of cancer surgeries, and have diverse roles in cancer cell biology. That means the roles of dexmedetomidine on the tumor-progressive factors were still complex and non-uniform. It is still cautious to make a conclusion concerning whether dexmedetomidine is harmful for some kinds of cancer patients. More future clinical trials should be held to provide more specific information. This may lead to optimization in the strategy of anesthesia in cancer patients in the future.

Data Sharing Statement

The data presented in the article could be requested by consulting the corresponding author.

Ethical Approval

No ethical approval was required for the review.

Author Contributions

Yang Hu, Meiling Gao performed the conception of this review; Yuting Guan, Huixia Wei, Zhiqian Dou, Dexi Liu contributed to the related article collection; Qiang Cai, Meiling Gao, Linsheng Huang, Guoqing Liu performed reviewing the related articles and wrote the review. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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