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Trial watch: dexmedetomidine in cancer therapy

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ABSTRACT

Dexmedetomidine (DEX) is a highly selective α_2 -adrenoceptor agonist that is widely used in intensive and anesthetic care for its sedative and anxiolytic properties. DEX has the capacity to alleviate inflammatory pain while limiting immunosuppressive glucocorticoid stress during major surgery, thus harboring therapeutic benefits for oncological procedures. Recently, the molecular mechanisms of DEX-mediated anticancer effects have been partially deciphered. Together with additional preclinical data, these mechanistic insights support the hypothesis that DEX-induced therapeutic benefits are mediated *via* the stimulation of adaptive anti-tumor immune responses. Similarly, published clinical trials including ancillary studies described an immunostimulatory role of DEX during the perioperative period of cancer surgery. The impact of DEX on long-term patient survival remains elusive. Nevertheless, DEX-mediated immunostimulation offers an interesting therapeutic option for onco-anesthesia. Our present review comprehensively summarizes data from preclinical and clinical studies as well as from ongoing trials with a distinct focus on the role of DEX in overcoming (tumor microenvironment (TME)-imposed) cancer therapy resistance. The objective of this update is to guide clinicians in their choice toward immunostimulatory onco-anesthetic agents that have the capacity to improve disease outcome.

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Introduction

Dexmedetomidine (DEX) is an α_2 -adrenergic receptor (α_2 -AR) agonist broadly used in clinical practice for its sedative and analgesic effects. DEX is the dextrorotatory S-enantiomer of medetomidine (4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1 H-imidazole),¹ an imidazole with high affinity and selectivity for the α_2 -AR as compared to α_1 -AR (α_2 : α_1 affinity ratio of 1260:1) (Figure 1a). Similar to clonidine, DEX exhibits a 5 to 10 times higher specificity and selectivity for the α_2 -AR expressed in the central nervous system as compared to the periphery.² The α_2 -AR belongs to the group of G-protein coupled receptors (GPCRs). Upon ligation, α_2 -AR agonists induce a conformational change from the GDP-bound to the GTP-bound state, inducing the efflux of potassium and a consequent hyperpolarization of the plasma membrane. Membrane hyperpolarization in turn inhibits the gating of voltage-dependent Ca^{2+} channels, thus blocking the release of neurotransmitters (Figure 1b). By binding to presynaptic α_2 -ARs, DEX also exerts a negative feedback compromising the release of norepinephrine and inhibiting neurons located in the locus coeruleus of the brainstem involved in the maintenance of consciousness³ (Figures 2a,c). In contrast to benzodiazepines and intravenous hypnotics such as propofol or etomidate, DEX has no direct action on gamma-aminobutyric acid (GABA) receptors, explaining its remarkable property of inducing sedative effects without forcing respiratory depression, but instead mimicking natural sleep, thus avoiding respiratory arrest and preventing post-anesthetic amnesia. However, DEX can disinhibit the ventrolateral preoptic

nucleus (VLPN), thus indirectly promoting the release of GABA and activating downstream signaling such as the inhibition of the tuberomammillary nucleus involved in arousal⁴ (Figure 2a). DEX also acts on α_2 -ARs expressed in the peripheral system and the dorsal horn of the spinal cord, thus inhibiting the release of nociceptive molecules such as norepinephrine, substance P and calcitonin gene-related peptide, in turn impairing pain conduction⁵⁻⁷ (Figures 2a,d). Furthermore, DEX stimulates a systemic increase of acetylcholine, which acts on cholinergic receptors thus attenuating neuro-inflammation and hyperalgesia provoked by neuropathic pain⁸⁻¹¹ (Figure 2d). Moreover, DEX-mediated non-narcotic analgesia does not impact on opioid receptors and is therefore non-addictive.¹² Nevertheless, by acting on post-synaptic α_2 -ARs, DEX can modulate hemodynamic responses and consequently induce dose-dependent vasoconstriction- or vasodilatation-mediated side effects including transient hypertension, and hypotension, respectively. In addition, in some cases, DEX was reported to induce reflex bradycardia or cause an atrioventricular block, that can lead to asystole, especially after intravenous loading, altogether encouraging its administration by continuous and progressive infusion^{13,14} (Figure 2a).

DEX can be administered through various injection routes such as intranasal, sublingual, transmucosal, subcutaneous or intramuscular but is most often infused intravenously. In the circulation, DEX is tightly bound to plasma proteins (94%) and unfolds its sedative and analgesic effects within a few minutes after intravenous infusion, with an elimination half-life

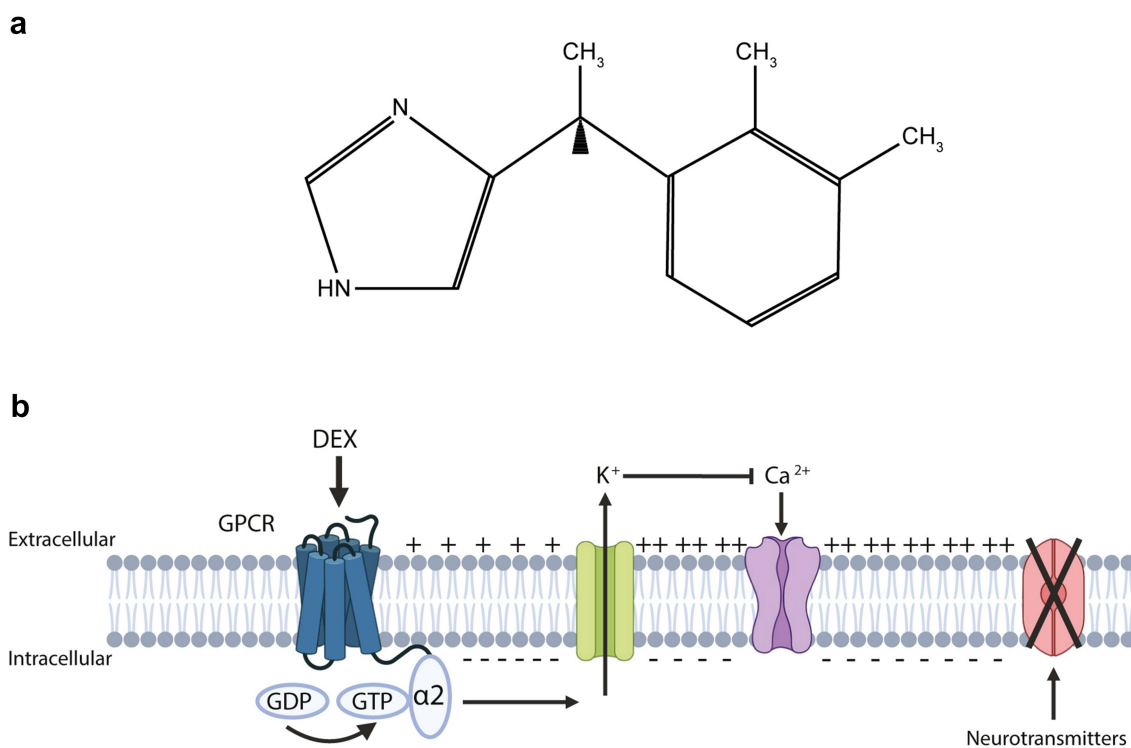


Figure 1. Dexmedetomidine: chemical formula and mode of action. (a) Chemical formula of dexmedetomidine (4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole). (b) Upon ligation to $\alpha 2$ -adrenoceptor, a G-protein coupled receptor (GPCR), dexmedetomidine (DEX) provokes a conformational change from the GDP-bound to the GTP-bound state, inducing the efflux of potassium and a hyperpolarization of the plasma membrane. Membrane hyperpolarization in turn inhibits the gating of voltage-dependent Ca^{2+} channels, blocking the release of neurotransmitters. Created with <https://www.BioRender.com>

between 2–4 h. DEX is metabolized in the liver and eliminated by renal clearance, altogether necessitating particular precautions in case of preexisting hepatic and renal dysfunctions.¹⁵

At the beginning DEX was clinically employed for the treatment of acute agitation, schizophrenia and bipolar disorders. In addition, DEX was shown to be particularly useful to reverse the hyperactive effects of amphetamines and cocaine abuse. Following the approval by the Food and Drug Administration (FDA) in 1999 and by the European Medicines Agency (EMA) in 2011, DEX was employed for short sedation (less than 24 h) of critically ill patients under mechanical ventilation. In clinical intensive care practice, the use of DEX was extended to the maintenance of artificial coma with the aim to decrease the extubation time during the recovery phase. Currently, anesthesiologists also employ DEX as a sedative agent for awake procedures such as fibroscopic intubation or as a local adjuvant in spinal anesthesia or nerve block. In general anesthesia, DEX is employed for opioid-free-anesthesia (OFA) combining DEX, ketamine, lidocaine, and magnesium to decrease the requirement for the use of opioids, thus minimizing the occurrence of nausea and hallucinations during the post-operative period.^{16,17}

Moreover, DEX was described to act on α -ARs located on the surface of cancer cells, thereby exerting both pro- and antitumor effects (Figure 2b). Recent publications indicate that DEX minimizes surgical stress responses, thus inducing immunostimulatory effects that positively impact anticancer immunity. Here, we summarized preclinical and clinical data as well as ongoing trials focusing on DEX-mediated anticancer

effects with the main objective of guiding clinicians in their surge for the ideal oncological anesthesia protocols.

Preclinical studies

The expression of $\alpha 2$ -ARs at the plasma membrane surface of many types of cancer cells such as breast carcinoma, non-small cell lung cancer and neuroglioma^{18,19} led to the hypothesis that DEX may exert direct pharmacological effects on malignant cells.

Initial preclinical investigations showed a cytoprotective effect of DEX in malignant cells under oxygen-glucose deprivation (OGD). DEX prevented OGD-induced cellular injuries by triggering anti-apoptotic PI3K-AKT signaling and by up-regulating the expression of hypoxia and DNA damage response genes including hypoxia-inducible factor 1 α (HIF-1 α) and vascular endothelial growth factor (VEGF).²⁰ Furthermore, DEX was found to stimulate the hypoxia-induced proliferation of human lung and colorectal carcinoma cells by promoting the expression of survivin, matrix metalloproteinase (MMP) 2 and 9, HIF-1 α ²¹ and favoring tumor angiogenesis in human hepatocellular carcinoma cells.²² Under normoxic conditions, low-dose (10 $\mu\text{g}/\text{kg}$) of DEX induced HIF-1 α /VEGF-dependent tumor angiogenesis in orthotopically established hepatocellular carcinoma in rodents, whereas high-dose (25 $\mu\text{g}/\text{kg}$) caused cytotoxic effects.²² Additional preclinical work showed that DEX (in a concentration range of 1 nM to 10 μM) promoted the proliferation, migration and survival of tumor cells^{18,19} by

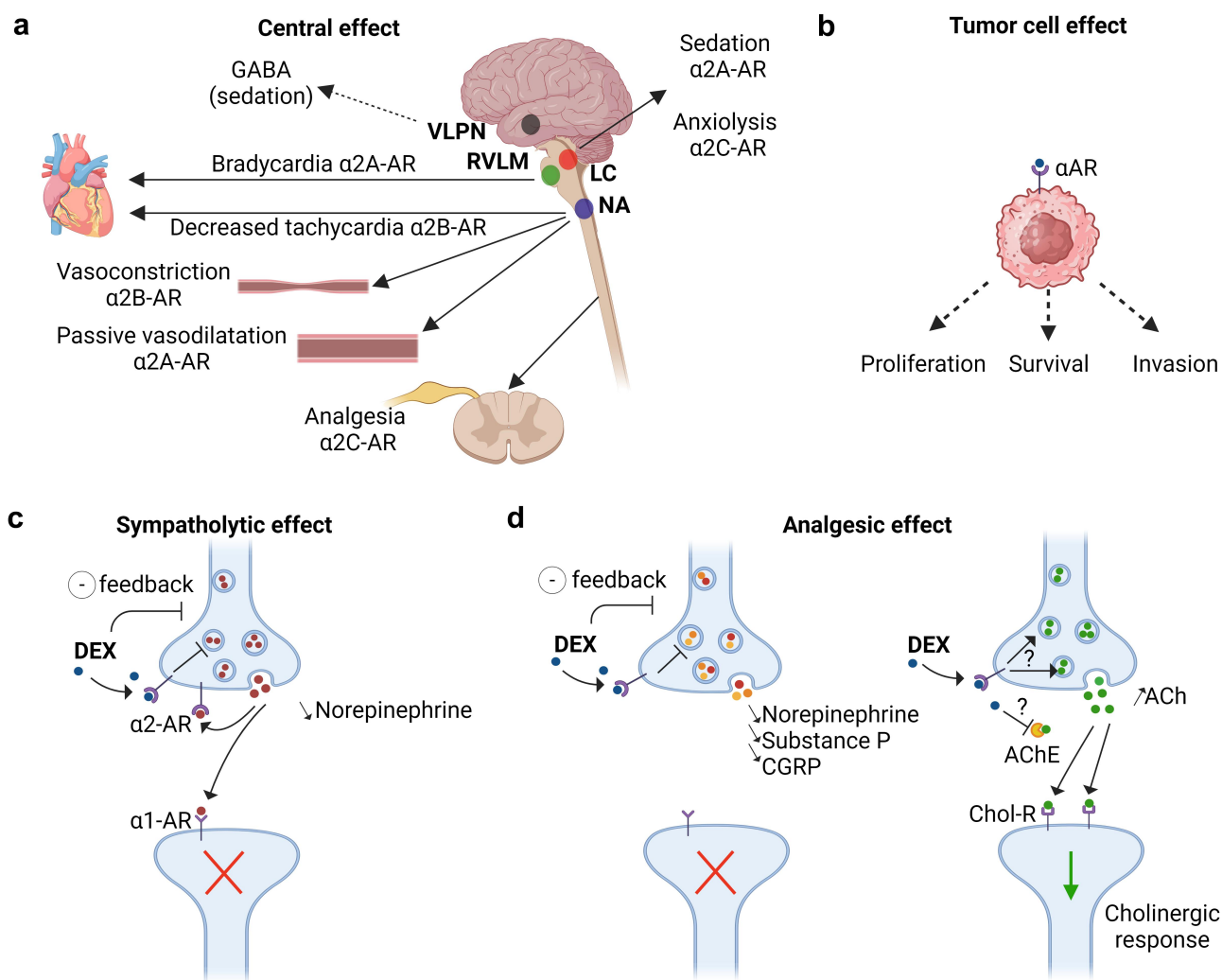


Figure 2. Sympatholytic and analgesic effects of dexmedetomidine through the α_2 -adrenoceptors. (a, b, c) α_2 -adrenoceptors (α_2 -AR) are composed of four subtypes: α_2A , α_2B , α_2C , and α_2D . By acting on α_2A -AR and α_2C -AR in the locus coeruleus (LC), dexmedetomidine (DEX) decreases the release of norepinephrine from presynaptic neurons inducing sedative and anxiolytic effects. DEX could also disinhibit the ventrolateral preoptic nucleus (VLPN) promoting the release of GABA, which in turn suppresses the tuberomammillary nucleus involved in arousal. The sympatholytic action of DEX on α_2A -AR in the rostral ventrolateral medulla (RVLM) and on α_2B -AR in the nucleus ambiguus (NA) decreases the heart rate. On the vessels, DEX induces a transient vasoconstriction through α_2B -AR, while the link to α_2A -AR rather triggers a vasodilatation leading to hypotension. Moreover, DEX was described to act on α -ARs located on the surface of cancer cells, thereby exerting potential both pro- or antitumor effects. (d) DEX exhibits its analgesic properties by binding to the α_2A -AR receptors in the dorsal horn of the spinal cord thus decreasing the release of nociceptive molecules such as norepinephrine, substance P and calcitonin gene-related protein (CGRP). In addition, DEX reduces neuropathic pain-induced inflammation and hyperalgesia by increasing the rate of acetylcholine (ACh) and cholinergic signaling through cholinergic receptors (Chol-R). The exact mechanism by which DEX increases the level of ACh, either through α_2 -AR mediated positive feedback or by inhibiting acetylcholinesterase (AChE) in the synaptic cleft, is unclear. Created with <https://www.BioRender.com>

upregulating anti-apoptotic proteins such as BCL-2, BCL-XL, thus retarding cell death, as well as the cyclins A, D and E, that stimulate cell division.¹⁹ DEX was also reported to activate the migration of malignant cells through the signal transducer and activator of transcription 3 (STAT3)-mediated secretion of the transmembrane protease serine 2 (TTPRSS2), a member of the transmembrane serine protease family involved in tumor growth and proliferation.²³ In addition, DEX was reported to promote the secretion of the proinflammatory cytokine IL-6 *in vitro*²⁴ and to stimulate tumor growth and the occurrence of secondary lesions in several solid tumors established in rodents.^{24–26} DEX-induced effects were abolished by the co-injection of yohimbine, an α_2 -AR antagonist, while phenoxybenzamine, an α_1 -AR antagonist had no effect, suggesting that DEX-mediated specific protumor effects through α_2 -AR^{25,26}

(Table 1). Based on these premises, DEX could trigger protumorigenic signaling pathways increasing the supplementation of oxygen to the tumor through neoangiogenesis, encouraging the invasion of distant organs by facilitating the migration of malignant cells through the extracellular matrix with the activation of the specific enzymes MMP, and sustaining survival and tumor cell proliferation through the activation of cyclins and anti-apoptotic molecules.

Conversely, more recent publications rather support the idea that DEX compromises tumor growth both *in vitro* and *in vivo*.^{27–39} Specific underlying molecular mechanisms have been unveiled. *In vitro*, DEX was found to upregulate pro-apoptotic BAX and activate effector caspase but downregulate the anti-apoptotic protein BCL-2.^{28,30–32,34,39} Furthermore, DEX was shown to promote oxidative stress and iron

Table 1. Preclinical research describing protumor effects of dexmedetomidine.

Date	Cancer type	Cell lines Animal model	Effects on cancer	Mode of action	Doses	Ref
2012	Glioma	Rat glioma C6	Protected cell viability of cells exposed to OGD	Anti-apoptotic properties, I2 imidazoline receptor-PI3K/AKT pathway activation, up-regulation of HIF-1 α , VEGF and RTP801 expression	<i>In vitro</i> (0.01–10 μ M)	20
2017	Breast	Human breast cancer MDA-MB-231	Increased cell proliferation, migration and invasion in a dose-dependent manner; increased volume of xenograft tumor; clonidine mimics the effects of DEX	Enhanced ERK phosphorylation; upregulated α 2-AR	<i>In vitro</i> (0.01, 0.1, 1 μ M)	18
2018	Breast Colon Lung	Rat breast carcinoma MADB 106; mouse Lewis Lung carcinoma 3LL; mouse colon carcinoma CT26; MADB 106 lung metastases model in F344 rats; 3LL lung metastases model in C57Bl/6 mice; CT26 liver metastases model in BALB/c mice	Increased tumor-cell retention, growth of metastases and metastatic burden in different stress models	Effects reversed by yohimbine but not by phenoxybenzamine	<i>In vivo</i> (2, 5, 20, 100 μ g/kg/h for 6–12 h)	25
2018	Lung Neuro-glioma	Human lung carcinoma A549; human neuroglioma H4	Promoted cell proliferation and migration	Increase in cyclins A, D, E and Ki67; upregulated anti-apoptotic proteins (Bcl-2, Bcl-xl); effects reversed by atipamezole	<i>In vitro</i> (0.001–10 nM)	19
2018	Lung	Mouse Lewis Lung carcinoma LLC; 3LL lung metastases model in C57Bl/6 mice	Promoted lung metastases	Increased M-MDSC and promoted VEGF by α 2-AR	<i>In vivo</i> (10 μ g/kg/h)	26
2019	Colorectal Lung	Human lung carcinoma A549; human colorectal carcinoma HCT116	Enhanced the progression of cancer cells	Upregulated survivin, MMP-2, MMP-9 and HIF-1 α in response to hypoxia	<i>In vitro</i> (1 nM)	21
2020	Breast	Human breast cancer MCF-7, MDA-MB-231	Increased migration	Secreted TMPRSS2 in exosomes through Rab11 in dose and time-dependent manner; upregulated TMPRSS2 <i>via</i> α 2-AR/STAT3 signaling	<i>In vitro</i> (0.01–1 μ M)	23
2020	Liver	Human hepatocarcinoma Huh7; mouse hepatocarcinoma Hepa1–6; human hepatic stellate LX-2; Hepa1–6 subcutaneous and orthotopic HCC model in C57Bl/6 mice; H22 and pHSC subcutaneous HCC in BALB/c mice	Promoted proliferation, metastasis, tumor growth and hepatic/pulmonary metastasis in liver fibrosis model	α 2-AR expressed on activated hepatic stellate cells (aHSC) but rarely on hepatocellular carcinoma (HCC); induced IL-6 secretion from aHSC; no action on quiescent HSC cells; promoted STAT3 activation of HCC in presence of aHSC;	<i>In vitro</i> (10 μ M); <i>in vivo</i> (10 μ g/kg)	24
2022	Liver	Human hepatocellular carcinoma SMMC-7721, MHCC97-H; BALB/c nude mice (orthotopic hepatic carcinoma)	<i>In vitro</i> : promoted angiogenesis; <i>in vivo</i> : low dose 10 μ g/kg favored angiogenesis but not high dose 25 μ g/kg (opposite effect)	<i>In vitro</i> : activation of HIF-1 α /VEGFA; <i>in vivo</i> : activation of HIF-1 α /VEGFA pathway	<i>In vitro</i> (0.5 μ g/ml); <i>in vivo</i> (10 μ g/kg, 25 μ g/kg for 14 days)	22

Abbreviations: aHSC, activated hepatic stellate cells; AR, adrenoceptor; ERK, extracellular regulated kinase; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; IL, interleukin; MDSC, myeloid-derived suppressive cells; MMP, matrix metalloproteinase; OGD, oxygen-glucose deprivation; PI3K/Akt, phosphoinositide 3 kinase/protein kinase B; STAT3, signal transducer and activator of transcription 3; TMPRSS2, transmembrane protease serine 2; VEGF, vascular endothelial growth factor.

production in human gastric carcinoma cells leading to the induction of ferroptotic cell death.^{38,40,41} In addition, DEX impairs cellular migration by decreasing vimentin expression and increasing the adherence of tumor cells *via* increased expression of E-cadherin. Moreover, DEX inhibits the proliferation of malignant cells by provoking cell cycle arrest *via* a decrease in cyclin D1 expression.^{28,32} Some studies also reported an extracellular regulated kinase (ERK) 1/2-dependent inhibition of the c-MYC oncogene, which is amplified in various types of cancer and promotes invasiveness and proliferation.^{29,34} It is worth noting that most DEX-mediated antitumor effects are provoked by epigenetic changes such as the modification of the expression of non-coding RNAs including miRNAs, circRNAs and lncRNAs. Thus, DEX activates the miR-143-3p/epidermal growth factor receptor (EGFR) pathway substrate 8 axis,²⁸ increases miR-493-5p, which targets RASL11B implicated in cancer development,³⁰ decreases the expression of miR-1307,³¹ upregulates miR-185,

which inactivates the Sry (sex determining region Y)-box 9 (SOX9)/Wnt/B-catenin pathway³² and miR-520a-3p that targets the metastases-inducing gene *Yod1* coding for the deubiquitinating enzyme YOD1.³³ DEX regulates circular RNAs, thereby affecting the circ -0003340/miR-198/HMGA2³⁵ and circ0008035/miR-302a/E2F7 axes.³⁸ Moreover DEX reduces the expression of the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), thus reducing cellular viability *in vitro* and decreasing tumor growth *in vivo*³⁶ (Figure 3). Taken together, these recent data argue that DEX could also mediate direct anti-tumor effects through a variety of mechanisms including epigenetic modifications, the induction of apoptotic and ferroptotic cell death,⁴² a decrease in tumor cell migration *via* the expression of E-cadherin and the depletion of vimentin, and an arrest in cell cycle through the cessation of cyclin D1 synthesis.

In addition to its direct effect on cancer cells, DEX was shown to alleviate stress and inflammatory responses. *In vitro*, DEX

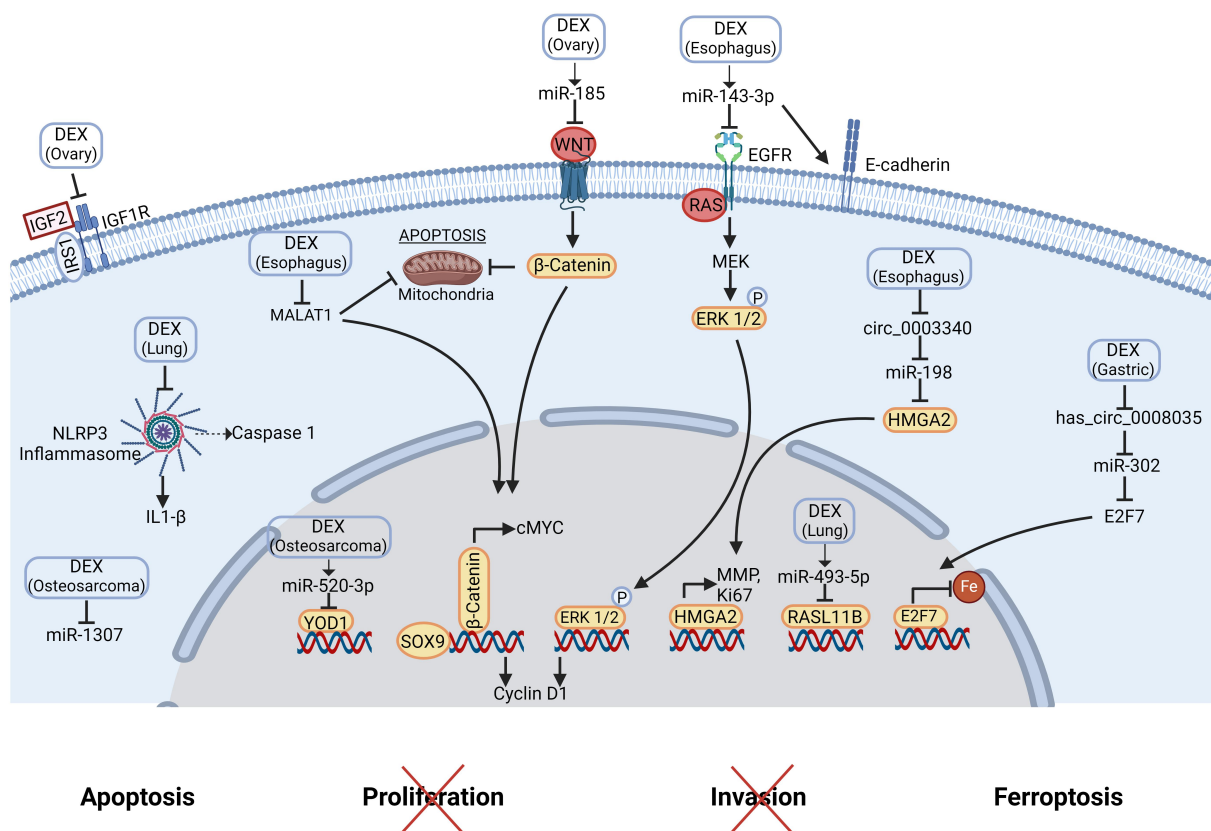


Figure 3. Molecular mechanisms of dexmedetomidine-mediated anti-tumor effects. DEX suppresses esophagus cancer progression via miR-143-3p/EGFR, by repressing c-MYC, MALAT1 and ERK1/2 expression, by increasing E-cadherin expression, and by regulating circ -0003340/miR-198/HMGA2. Furthermore, DEX promotes ferroptosis in gastric adenocarcinoma through the inhibition of the circ0008035/miR-302a/E2F7 axis. It decreases the proliferation and migration of human osteosarcoma cells and triggers apoptosis via the up-regulation of miR-520a-3p that targets YOD1 and the inhibition of miR-1307. Moreover, DEX inhibits lung tumor growth and favors apoptosis via an up-regulation of miR-493-5p, which targets RASL11B and inhibits aberrant inflammasome activation. DEX induces ovarian cancer cell apoptosis via the up-regulation of miR-185 that inactivates SOX9/Wnt/B-catenin and decreases the invasion and migration by inhibiting IGF2 pathway. Created with <https://www.BioRender.com> Abbreviations: DEX, dexmedetomidine; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; HMGA2, high mobility group AT-hook 2; IGF, insulin-like growth factor; IL, interleukin; IRS1, insulin receptor substrate 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MMP, matrix metalloproteinase; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; SOX9, Sry (Sex determining region Y)-box 9

exposure reduces OGD-induced inflammation by attenuating the release of IL-1 β , IL-6 and tumor-necrosis factor (TNF)- α .⁴³ In a murine model of surgical stress, DEX significantly reduced the level of cortisol and TNF- α in the postoperative period, correlating with lower tumor burden.⁴⁴ In metastatic lung tumor xenografts, the continuous injection of DEX for 14 days significantly repressed the release of inflammatory cytokines including IL-1 β , IL-18, TNF- α and inhibited inflammasome activation in tumor tissues by impinging on the expression of nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3), carnitine palmitoyltransferase 1A (CPT1A), thioredoxin (TRX)-interacting protein (sTXNIP), adapter protein apoptosis associated speck-like protein containing a CARD (ASC) and caspase 1.³⁷ Interestingly, these readouts illustrate that DEX might induce indirect anti-tumor effects by decreasing surgical inflammatory stress, which favors the proliferation and survival of tumor cells. If confirmed in clinical practice, these results could suggest that DEX is an outstanding adjuvant for controlling protumor inflammation in the per-operative period optimally. DEX was also shown to increase IFN- γ expression and to stimulate effectors of both innate and adaptive anticancer immunity such as natural killer (NK) cells^{37,44} in ovarian and lung cancer

in vivo. Moreover, DEX fosters tumor infiltration by CD4⁺, CD8⁺ and NK cells in murine colon adenocarcinoma.³⁹ Finally, DEX could also elicit an immune anti-tumor response by stimulating specific anti-tumor immune effectors to recognize and kill malignant cells and infiltrate tumor bed and its microenvironment^{45,46} (Table 2).

In sum, these preliminary findings suggest a dual dose-dependent role of DEX. In thus far that low doses of DEX would trigger tumorigenic pathways able to support tumor growth, while clinically relevant concentrations of DEX would facilitate cytotoxic responses and the recruitment of immune effectors against malignant cells.

Published clinical studies

Thirty-one clinical studies (19 randomized controlled trials (RCT), 5 prospective studies, 5 retrospective studies, 2 meta-analyses) investigated the biological effects of DEX administered during oncological surgeries. Among these, four trials attributed a potentially pro-tumorigenic role to DEX. In the study of Liu *et al.*, 29 women undergoing simple or radical mastectomy with sentinel lymph node biopsy were randomly

Table 2. Preclinical research describing antitumor effects of dexmedetomidine.

Date	Cancer type	Cell lines Animal model	Effects on cancer	Mode of action	Doses	Ref
2019	Ovary	Rat ovarian adenocarcinoma; NUTU-19; NUTU-19 subcutaneous ovarian model in F344 rats	Improved immune function; inhibited invasion and migration at high dose	Decreased TNF- α , IGF2, IGF1R, IRS1; increased IL-2, IFN- γ , CD4 ⁺ and CD8 ⁺ , CD4 ⁺ /CD8 ⁺ ratio; inhibited IGF2 pathway	<i>In vivo</i> (0.2, 1, 5 μ g/kg/h for 15 days)	27
2020	Esophagus	Human esophageal carcinoma KYSE150, Eca-109; KYSE150 xenograft model	Decreased proliferation and metastasis; suppressed cancer progression	Induction of apoptosis; regulation of miR-143-3p/EGFR pathway substrate 8	<i>In vitro</i> (1 μ M) <i>In vivo</i> (NA)	28
2020	Glioma	Human glioma U251, U87MG	Decreased cell invasion at 50 nM (and not at 10 nM); cisplatin toxicity was attenuated by 10 nM DEX but enhanced by 50 nM DEX	Increased p-ERK1/2, PI3K and p-AKT; decreased in Ca ²⁺ concentration	<i>In vitro</i> (10, 50 nM)	29
2021	Bone	Human osteosarcoma MG-63	Decreased proliferation and migration	Decrease in miR-1307 expression; triggered apoptosis in dose-dependent manner	<i>In vitro</i> (25, 50, 100 ng/ml)	31
2021	Bone	Human osteosarcoma HOS, U2OS	Decreased cell viability, proliferation and adhesion	Promoted apoptosis <i>via</i> up-regulation of miR-520a-3p that targets YOD1	<i>In vitro</i> (1, 10, 100 ng/ml)	33
2021	Esophagus	Human esophageal carcinoma; Eca109	Inhibited viability and proliferation	Promoted apoptosis by repressing c-MYC and ERK1/2 protein expression	<i>In vitro</i> (1, 10, 100, 1000 ng/ml)	34
2021	Lung	Human lung adenocarcinoma A549	Inhibited tumor growth	Favored apoptosis <i>via</i> up-regulation of miR-493-5p, which targets RASL11B	<i>In vitro</i> (1 nM)	30
2021	Ovary	Human ovarian adenocarcinoma; SK-OV-3-Luc cells; BALB/c nude mice	<i>In vivo</i> model of surgery = lower tumor burden at 4 weeks in DEX group	In the DEX group = at day 3, faster NK cell activity, lower cortisol level, lower TNF- α level	<i>In vitro</i> (0.1, 0.5, 1, 5 μ g/ml); <i>in vivo</i> (12 μ g/kg/j for 4 weeks)	44
2021	Ovary	Human ovarian cancer SKOV3, HO-8910; BALB nude mice	Inhibited cell growth	Decrease in cyclin D1 and c-MYC and increased apoptosis (enhanced cleaved caspase 3 and Bax, decreased Bcl-2) in dose-dependent manner <i>via</i> the up-regulation of miR-185 that inactivates SOX9/Wnt/B-catenin pathway both <i>in vitro</i> and <i>in vivo</i>	<i>In vitro</i> (1–100 nM); <i>in vivo</i> (1 bolus, 100 nM)	32
2022	Esophagus	Esophageal cancer cells KYSE410, Eca109; BALB/c nude mice	Decreased proliferation and invasion	Regulation of circ -0003340/miR-198/HMGA2	<i>In vitro</i> (50, 100, 200 ng/ml); <i>in vivo</i> (for 3 days)	35
2022	Esophagus	Human esophageal carcinoma Eca109, TE-1; nude mice	Inhibited the viability and decreased tumor growth	Decrease in MALAT1 expression (dose dependent)	<i>In vitro</i> 1 ng/ml-1 mg/ml; <i>in vivo</i> 0.5 mg/kg every 5 days	36
2022	Pheochromocytoma	Rat pheochromocytoma PC12	Inhibited OGD reperfusion	Inhibited IL-1 β , TNF- α and IL-6 release; decreased apoptosis (downregulated Bax and caspase-3 by increasing miR-17-5p)	<i>In vitro</i> (1, 10, 50 μ M)	43
2023	Breast Colorectal Fibro-sarcoma Lung	Murine breast cancer EO771, 4T1; murine lung cancer LAP0297; murine Lewis Lung Carcinoma LLC; murine fibrosarcoma MCA205; murine colon adenocarcinoma MCA38, CT26	Inhibited tumor growth	Promoted apoptosis for MCA38 and CT26 tumors; increased tumor infiltration by CD4 ⁺ , CD8 ⁺ , NK in MCA38 tumors	<i>In vivo</i> (1 bolus 25 μ g/kg)	39
2023	Gastric	Human gastric adenocarcinoma; SNU-1, AGS; BALB/c nude mice	Decreased cell viability and tumor growth	Increased apoptosis and ROS production; promoted ferroptosis through circ0008035/miR-302a/E2F7 axis;	<i>In vitro</i> (0.1–100 μ M); <i>in vivo</i> (0.5, 1, 2 g/kg for 15 days)	38
2023	Lung	Human lung adenocarcinoma A549; BALB/c nude mice	Inhibited tumor growth	Decreased IL-1 β , TNF- α , IL-10 and IL-18; increased NK cell activity and IFN- γ expression; suppressed inflammasome (decrease in NLRP3, CPT1A, TXNIP, ASC, IL-1 β and caspase 1)	<i>In vivo</i> (20 μ g/kg/j for 14 days)	37

Abbreviations: ASC, adapter protein apoptosis associated speck-like protein containing a CARD; CPT1A, carnitine palmitoyltransferase 1A; DEX, dexmedetomidine; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; HMGA2, high mobility group AT-hook 2; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; IRS1, insulin receptor substrate 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; NK, natural killer; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; OGD, oxygen-glucose deprivation; PI3K/Akt, phosphoinositide 3 kinase/protein kinase B; ROS, reactive oxygen species; SOX9, Sry (Sex determining region Y)-box 9; TNF, tumor necrosis factor; TXNIP, thioredoxin (TRX)-interacting protein.

allocated to receive either DEX or normal saline in addition to general anesthesia. Then, human breast cancer MCF-7 cells were cultured and exposed to the serum of patients. The proliferation, migration and invasion were significantly accelerated in presence of sera from DEX-treated patients as compared to control sera.⁴⁷ In a similar study, 124 patients who underwent radical mastectomy were randomly assigned to be anesthetized with or without an intravenous infusion of DEX. The serum levels of anti-tumor immune effector NK cells and CD8⁺ T lymphocytes were decreased, while an important increase in inflammatory markers (IL-6 and IL-10) were observed in the treatment group.⁴⁸ In a prospective trial, Su *et al.* investigated whether DEX could favor metastases by promoting myeloid-derived suppressor cells (MDSC) after lung surgery. In this study, 103 patients scheduled for thoracotomy were enrolled. Patients treated with DEX during the procedure had more circulating MDSC. In addition, these MDSC were more capable of inducing the synthesis of the neoangiogenic factor VEGF and suppressing T cell proliferation. *In vitro*, the expansion of MDSC isolated from lung cancer patients was enhanced in the presence of exogenous DEX, while the addition of yohimbine, an α 2-AR antagonist, inhibited the DEX-induced proliferative effect, suggesting the involvement of α 2-AR in the DEX-mediated protumor effect.²⁶ Finally, a propensity score-matched retrospective study evaluated the impact of intraoperative DEX administered during lung cancer surgery on survival. No association was observed between DEX and recurrence-free survival. However, multivariate analysis indicated that DEX could reduce overall survival.⁴⁹ One additional retrospective study and two RCTs investigated whether DEX injected during hyperthermic intraperitoneal chemotherapy (HIPEC) for appendiceal carcinomatosis, prostatectomy or hysterectomy could improve postoperative oncological outcome, yet failed to detect improved progression-free, recurrence-free or overall survival.^{50–52}

Conversely, 25 trials indicate that DEX exhibits beneficial effects on oncological patients. Notably, DEX has the ability to alleviate the immunosuppressive glucocorticoid stress produced by surgery. In the double-blind RCT of Kim *et al.*, 143 patients were randomly assigned to receive continuous infusion of DEX or normal saline during thoracic surgery. Here, the inflammatory cytokines IL-8 and IL-10 were significantly lower 1 h after the intervention.⁵³ Similarly, in the prospective study by Zhou *et al.*, the group treated with a loading dose of DEX had significantly lower circulating level of IL-8 and TNF- α after lung cancer surgery. This effect was directly correlated to the downregulation of miR-10a.⁵⁴ Three RCTs and one retrospective trial studied intraoperative immune effects of DEX during gastric, esophageal and ovarian cancer surgery. The authors observed a stable level^{55,56} or decline of C-reactive protein (CRP), IL-6, IL-10 or TNF- α in the treated group.^{57,58} Two meta-analyses including 17 RCTs and 11 RCTs focused on the employment of DEX during major digestive and lung cancer procedures respectively. Both meta-analyses concluded on a DEX-induced decrease in protumor and inflammatory cytokines such as CRP, IL-6, IL-8 and TNF- α .^{59,60} Many other studies dealing with the surgical removal of

various solid primary tumors demonstrated that patients receiving intravenous DEX during the perioperative period had an attenuated increase in glucocorticoid stress compared to the control group.^{61–70} Interestingly, two trials observed that DEX affected the activity of the corticotropic axis by attenuating the concentrations of circulating catecholamines and adrenocorticotrophic hormone (ACTH).^{53,71} DEX also compromised the synthesis of protumor biomarkers, and key regulators of invasiveness. In the RCT by Ren *et al.*, 132 non-small cell lung cancer patients operated with video-assisted thoracic surgery were enrolled and received DEX, lidocaine, DEX+lidocaine or saline solution. Patients of the DEX group produced significantly less neutrophil extracellular traps (NETs), MMP-3, MMP-9 and VEGF involved in cancer-associated inflammation, angiogenesis and the migration of residual cancer cells to the distant organs. DEX-mediated effects were further potentiated by concomitant use of lidocaine.^{72–74} Similarly, in the peripheral blood of patients undergoing hysterectomy under DEX infusion, Cho *et al.* observed an increase in the cytolytic cytokine IFN- γ , which is produced by the T lymphocytes to kill residual cancer cells.⁵² In the RCT of Huang *et al.*, the authors included 34 patients for oral cancer surgery, known to be highly painful and inflammatory. Intraoperative infusion of DEX hampered the production of circulating immunosuppressive MDSCs, thus decreasing escape from immunosurveillance.^{75–77} Some trials noticed that DEX limited the decrease of immune effectors such as dendritic cells (DC), B, T and NK cells and the increase of regulatory T cells (Treg) as compared to control groups.^{61,63,72,75,78,79} The phase 3 RCT of Mohamed *et al.* explored whether wound infiltration of DEX together with the local anesthetic bupivacaine could decrease consumption of opioids and minimize glucocorticoid stress by optimal pain control during hysterectomy compared to the combination of ketamine and bupivacaine. The combination of DEX with ketamine significantly attenuated stress responses and had an opioid-sparing effect.⁸⁰ Taken together, these data can be interpreted to suggest that DEX impedes the immunosuppressive effects of surgical stress (Table 3). Conversely to preclinical investigations, accumulating clinical data reveal that during oncological procedures DEX alleviates surgical glucocorticoid stress and inflammation, both known to stimulate tumorigenic signaling and to impair the anticancer immune response. It is tempting to speculate that these characteristics might be employed to reinforce anticancer immunity during oncosurgery.⁸¹

Ongoing studies

Completed trials

Eight RCTs and one observational prospective study evaluated whether DEX used during primary tumor resection could indirectly impact on oncological outcome. Three studies have specifically investigated if DEX modified the immune system. The number and the activity of leucocytes, in particular T-cells and NK cells collected from the peripheral blood, were compared prior and after the administration of intravenous DEX during breast and uterine cancer surgery

Table 3. Published clinical trials studying the dexmedetomidine-induced biological effects potentially related to oncological outcome.

Cancer surgery	Study type	Study design	Biological effects of DEX	Ref
Appendiceal carcinoma-tosis	Retrospective	After matching: -study group DEX 0.075–0.3 µg/kg/h (<i>n</i> = 107); -control group NaCl + volatile (<i>n</i> = 107)	No association with improved PFS or OS	50
Brain	RCT	Forty children randomly allocated in: -study group DEX 0.5 µg/kg/h (<i>n</i> = 20); -control group NaCl (<i>n</i> = 20)	Decrease in CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , NK and B cells at 1 h and at POD1 compared to pre-anesthesia but less than control group (<i>p</i> < 0.05)	78
Breast	RCT	Twenty-nine women randomly allocated in: -study group DEX total dose 2 µg/kg (<i>n</i> = 16); -control group NaCl (<i>n</i> = 13)	Increase in proliferation, migration, and invasion of human breast cancer MCF-7 cells exposed to the serum of treated patients (<i>p</i> < 0.001)	47
Breast	RCT	One hundred and twenty-four patients randomly allocated in: -study group DEX 0.1 µg/kg/min (<i>n</i> = 62); -control group NaCl (<i>n</i> = 62)	Decrease in NK, CD8 ⁺ (<i>p</i> < 0.05); increase in CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , INF-γ, IL-2, IL-6, IL-10 (<i>p</i> < 0.05)	48
Colon	RCT	One hundred and forty-one patients randomly allocated in: -study group DEX 1 µg/kg/h (<i>n</i> = 72); -control group NaCl (<i>n</i> = 69)	Increase in CRP, IL-6 and IL-8 but less than control group Decrease in CD4 ⁺ , CD4 ⁺ /CD8 ⁺ , Th1 and increase in Treg but less than control group (<i>p</i> < 0.05)	61
Colon	Prospective	One hundred and seventy-six patients allocated in: -study group DEX 200 µg (<i>n</i> = 92); -control group NaCl (<i>n</i> = 84)	Decrease in CD3 ⁺ , CD4 ⁺ , CD4 ⁺ /CD8 ⁺ but less than control group (<i>p</i> < 0.05)	79
Colon	Prospective	One hundred and forty patients randomly allocated in: -study group DEX 1 µg/kg (loading dose) then 0.2–0.7 µg/kg/h (continuous) (<i>n</i> = 80); -control group NaCl (<i>n</i> = 60)	Increase in IL-6 but less than control group (<i>p</i> < 0.05)	62
Digestive	Meta-analysis	Seventeen studies (RCTs) = 1,619 patients	Decrease in CRP, TNF-α, and IL-6 (<i>p</i> < 0.01); increase in IL-10, CD4 ⁺ , CD4 ⁺ /CD8 ⁺ (<i>p</i> < 0.05)	59
Esophagus	RCT	Sixty-two patients randomly allocated in: -study group DEX 0.5 µg/kg (loading dose) then 0.2–0.4 µg/kg/h (continuous) then 0.06 µg/kg/h for 5 days (<i>n</i> = 31); -control group NaCl (<i>n</i> = 31)	No changes in leucocytes, IL-6, IL-10, CRP	55
Gastric	RCT	Fifty-five patients randomly allocated in: -study group DEX 0.2–0.7 µg/kg/h (<i>n</i> = 18); -control group Remifentanyl (<i>n</i> = 18); -control group Sufentanyl (<i>n</i> = 19)	Increase in serum levels of glucose, IL-6, β-EP and decrease in IFN-γ but less than other groups. Significant decrease in IL-10 and increase in IL-18 compared to other groups (<i>p</i> < 0.05)	70
Gastric	RCT	Seventy-four patients randomly allocated in: -study group DEX 0.2 µg/kg/h (<i>n</i> = 37); -control group NaCl (<i>n</i> = 37)	Increase in IL-1β, IL-6, TNF-α, NF-κB and CRP but less than control group (<i>p</i> < 0.05); decrease in T cells, CD4 ⁺ /CD8 ⁺ but less than control group (<i>p</i> < 0.05)	63
Gastric	Retrospective	One hundred and two patients allocated in: -study group DEX 0.5 µg/kg (loading dose) then 0.2–0.4 µg/kg/h (continuous) (<i>n</i> = 52); -control group NaCl (<i>n</i> = 50)	Increase in serum levels of cortisol, ACTH, TNF-α, IL-6 but less than control group (<i>p</i> < 0.05)	64
Gastric	RCT	Forty patients randomly allocated in: -study group DEX 0.5 µg/kg (loading dose) then 0.4 µg/kg/h (continuous) (<i>n</i> = 20); -control group NaCl (<i>n</i> = 20)	Increase in Th1/Th2 (<i>p</i> < 0.05); no significant increase in IL-6 and TNF-α	56
Gastric	RCT	Seventy-eight patients randomly allocated in: -study group DEX 0.1 µg/kg (loading dose) (<i>n</i> = 39); -control group NaCl (<i>n</i> = 39)	Decrease in IL-1β, IL-6, TNF-α, CRP (<i>p</i> < 0.05)	57
Lung	Prospective	One hundred and three patients allocated in: -study group DEX (median 122 µg [118–146] <i>i.v.</i>) (<i>n</i> = 51); -control group NaCl (<i>n</i> = 52)	Increase in M-MDSC (<i>p</i> < 0.0001) by α2-AR; MDSC more efficient in producing VEGF and in suppressing T cells proliferation (<i>p</i> < 0.01)	26
Lung	RCT	One hundred and sixteen patients randomly allocated in: -study group DEX 0.3 µg/kg/h (<i>n</i> = 58); -control group NaCl (<i>n</i> = 58)	Increase in serum levels of IL-6, IL-8, TNF-α, MDA but less than control group (<i>p</i> < 0.05)	65
Lung	RCT	Ninety patients randomly allocated in: -study group DEX 1 µg/kg/h (<i>n</i> = 30); -study group lidocaine (<i>n</i> = 30); -control group NaCl (<i>n</i> = 30)	Increase in IL-6 and TNF-α but less than control group (<i>p</i> < 0.05)	66
Lung	Retrospective	Ninety patients allocated in: -study group DEX 0.4 µg/kg/h (<i>n</i> = 48); -control group NaCl (<i>n</i> = 42)	Increase in serum levels of IL-8, IL-10, TNF-α but less than control group (<i>p</i> < 0.05)	67
Lung	Prospective	One hundred and twelve patients allocated in: -study group DEX 1 µg/kg (loading dose) then 0.3 µg/kg/h (continuous) (<i>n</i> = 59); -control group NaCl (<i>n</i> = 53)	Increase in serum levels of IL-8, TNF-α but less than control group (<i>p</i> < 0.05) correlated to the decrease in miR-10a expression; increase in MDA; decrease in SOD	54
Lung	RCT	One hundred and thirty-two patients randomly allocated in: -study group DEX 2 µg/kg/h (loading dose) then 0.5 µg/kg/h (continuous) then 0.25 µg/kg/h POD1 (<i>n</i> = 33); -study group lidocaine (<i>n</i> = 33); -study group DEX + lidocaine (<i>n</i> = 33); -control group NaCl (<i>n</i> = 33)	Decrease in the production of NETs, MMP-3, MMP-9, VEGF (<i>p</i> < 0.001), effects potentiated by lidocaine (<i>p</i> < 0.001); decrease in NK and IFN-γ/IL-4 but less than control group (<i>p</i> < 0.05)	72
Lung	Retrospective	After matching: -study group DEX (<i>n</i> = 251) (median 100 µg [57.47–140] <i>i.v.</i>); -control group NaCl (<i>n</i> = 251)	Decreased OS (HR = 1.25, 95%CI [1.03–1.59], <i>p</i> = 0.024)	49

(Continued)

Table 3. (Continued).

Cancer surgery	Study type	Study design	Biological effects of DEX	Ref
Lung	Meta-analysis	Eleven studies (RCTs) = 1,026 patients	Decrease in IL-6, IL-8 and TNF- α ($p < 0.01$)	60
Lung	RCT	One hundred and twenty patients randomly allocated in: -study group DEX 0.7 $\mu\text{g}/\text{kg}$ (loading dose) then 0.3 $\mu\text{g}/\text{kg}/\text{h}$ (continuous) ($n = 60$); -control group NaCl ($n = 60$)	Increase in serum levels of IL-1 β , IL-6, IL-10, TNF- α but less than control group ($p < 0.001$)	68
Lung	RCT	Forty patients randomly allocated in: -study group DEX 0.5 $\mu\text{g}/\text{kg}/\text{h}$ ($n = 20$); -control group NaCl ($n = 20$)	Increase in IL-8 but less than control group ($p < 0.05$)	69
Lung	RCT	One hundred and forty-three patients randomly allocated in: -study group DEX 0.5 $\mu\text{g}/\text{kg}/\text{h}$ ($n = 73$); -control group NaCl ($n = 70$)	Significant decrease in IL-8 ($p = 0.02$), IL-10 ($p = 0.002$), epinephrine and norepinephrine ($p < 0.001$)	53
Oral	RCT	Sixty-eight patients randomly allocated in: -study group DEX 0.5 $\mu\text{g}/\text{kg}$ (loading dose) then 0.4 $\mu\text{g}/\text{kg}/\text{h}$ (continuous) ($n = 34$); -control group NaCl ($n = 34$)	Decrease in CD3 $^+$, CD4 $^+$, CD4 $^+$ /CD8 $^+$, DCs but less than control group Significant decrease in MDSC ($p < 0.05$)	75
Ovarian	Retrospective	Three hundred and forty-three patients enrolled in: -study group DEX ($n = 169$) <i>i.v.</i> ; -control group MDZ ($n = 174$)	Decrease in serum levels of TNF- α and IL-6 ($p < 0.05$)	58
Prostate	RCT	One hundred and forty-six patients randomly allocated in: -study group DEX 0.2–0.7 $\mu\text{g}/\text{kg}/\text{h}$ ($n = 73$); -control group without opioid ($n = 71$)	No impact on RFS	51
Thyroid	Prospective	Ninety-six patients allocated in: -study group DEX 0.5 $\mu\text{g}/\text{kg}$ ($n = 49$); -control group NaCl ($n = 47$)	Decrease in MCP-1, ACTH, NE ($p < 0.001$)	71
Uterus	RCT	One hundred patients randomly allocated in: -study group DEX 0.4 $\mu\text{g}/\text{kg}/\text{h}$ (continuous) then 0.15 $\mu\text{g}/\text{kg}/\text{h}$ POD1 ($n = 50$); -control group NaCl ($n = 50$)	Increase in IFN- γ ($p = 0.003$); no difference on NK cell activity, inflammatory response; no difference in recurrence, metastases or death	52
Uterus	RCT	Ninety patients randomly allocated in: -study group DEX 2 $\mu\text{g}/\text{kg}$ + bupivacaine (local infiltration) ($n = 30$); -study group ketamine + bupivacaine (local infiltration) ($n = 30$); -control group bupivacaine (local infiltration) ($n = 30$)	DEX + bupivacaine: opioid-sparing effect; no increase in cortisol, prolactin and glucose compared to the control group ($p < 0.05$)	80

Abbreviations: ACTH, adrenocorticotropic hormone; AR, adrenoceptor; β -EP, β -enkephalin; CI, confidence interval; CRP, C-reactive protein; DC, dendritic cell; DEX, dexmedetomidine; HR, hazard ratio; IFN, interferon; IL, interleukin; *i.v.*, intravenous; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MDSC, myeloid-derived suppressor cells; MDZ, midazolam; MMP, matrix metalloproteinase; NA, non-applicable; NaCl, normal saline; NE, norepinephrine; NETs, neutrophil extracellular traps; NF- κ B, nuclear factor kappa B; NK, natural killer cell; OS, overall survival; PFS, progression-free survival; POD, postoperative day; RCT, randomized controlled trial; RFS, recurrence-free survival; SOD, superoxide dismutase; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

(NCT01692210; NCT03109990; NCT02896413). Three trials are measuring whether DEX modifies the inflammation response and notably the secretion of the protumoral cytokine IL-6 after major oncological procedures generating high level of neuroendocrine and cytokine response such as HIPEC for colon malignancies, gastrectomy and thoracotomy (NCT03370588; NCT03960775; NCT04007341). Two trials are determining if the continuous administration of DEX could influence the inflammatory response during and after robotic or laparoscopic gastrectomy and hysterectomy by assessing various inflammatory molecules such as CRP, IL-6, IL-8, IL-10 and TNF- α (NCT03960775; NCT02896413). Interestingly, the study NCT06037135 aims to assess if DEX can decrease the release of catecholamines and preserve hemodynamic stability during and after the removal of active pheochromocytoma. The phase 3 trial NCT04148599 is designed to compare intravenous DEX, intravenous lidocaine and placebo in reduction of inflammatory markers (IL-6 and TNF- α) and stress reaction (insulin, lactate) after pelvi-abdominal cancer resection. Two pilot studies focus on the potential impact of DEX on recurrence-free and overall survival after breast cancer interventions and HIPEC (NCT03109990; NCT03370588). The NCT02739958 trial is also exploring whether continuous infusion of DEX with the

intravenous hypnotic propofol can maintain the CD3 $^+$ T cells plasma level compared to the association of volatile hypnotic isoflurane with the opioid fentanyl during total laryngectomy surgery (Table 4). These completed trials focused on the potential impact of DEX on immune cells in particular in the context of minimally invasive procedures. In sum these results could lead to a reorientation of DEX toward specific protocols taking into consideration the level of surgical inflammation.

Ongoing trials

Eight ongoing RCTs plan to investigate whether intraoperative DEX might improve the prognosis of cancer patient. Four studies are designed to evaluate whether DEX decreases the incidence of recurrences and enhances the survival after oncological surgery (NCT05742438; NCT04106999; NCT03012971; NCT06030804). Whereas these trials compare DEX to placebo, the study NCT05742438 investigates whether DEX might be superior to intravenous infusion of lidocaine or to intrathecal injection of morphine to decrease the relapses as well as protumor factors secreted during oncological procedures such as MMP-2, MMP-9, IL-6 and VEGF. In addition, the phase 2–3 study NCT04106999 investigates whether DEX reduces postoperative inflammatory markers in

Table 4. Completed trials investigating the role of dexmedetomidine on cancer outcome.

Cancer	Design	Study type	Oncological endpoints	Potential endpoints related to cancer outcome	Phase	NCT number
Breast	DEX <i>i.v.</i> (1 bolus then continuous)	Obs		Pre- and postsurgical WBC count and function (NK cells)	NA	NCT01692210
Breast	DEX <i>i.v.</i> (1 bolus then continuous) vs placebo	RCT	RFS, OS	Number of CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD19 ⁺ , NK cells	NA	NCT03109990
Colon	DEX <i>i.v.</i> (continuous) vs placebo	RCT	Recurrence at 1 year	IL-6 level	NA	NCT03370588
Gastric	DEX <i>i.v.</i> (continuous) vs placebo	RCT		CRP level, cytokine level (IFN- γ , TNF- α , IL-6, IL-8, IL-10, HMGB1), WBC level	NA	NCT03960775
Larynx	DEX <i>i.v.</i> (continuous) + propofol vs isoflurane + fentanyl	RCT		CD3 ⁺ plasma level	NA	NCT02739958
Lung	DEX <i>i.v.</i> (1 bolus then continuous) vs placebo	RCT		IL-6 level	NA	NCT04007341
Pelvi-abdominal	DEX <i>i.v.</i> (1 bolus then continuous) vs lidocaine <i>i.v.</i> (continuous) vs placebo	RCT		Change in plasma levels of inflammatory mediators (IL-6, TNF- α), and stress markers (insulin, lactate)	3	NCT04148599
Pheochromocytoma	DEX <i>i.v.</i> (continuous) vs placebo	RCT		Level of catecholamines (epinephrine, norepinephrine)	NA	NCT06037135
Uterus	DEX <i>i.v.</i> (continuous) vs placebo	RCT		NK cell cytotoxicity; inflammatory response	NA	NCT02896413

Abbreviations: CRP, C-reactive protein; DEX, dexmedetomidine; HMGB1, high-mobility group box 1; IFN, interferon; IL, interleukin; *i.v.*, intravenous; NA, non-applicable; NK, natural killer; Obs, observational; OS, overall survival; RCT, randomized controlled trial; RFS, recurrence-free survival; TNF, tumor necrosis factor; WBC, white blood cells.

Table 5. Ongoing trials investigating the role of dexmedetomidine on cancer outcome.

Cancer	Design	Study type	Oncological endpoints	Potential endpoints related to cancer outcome	Phase	Status	NCT number
Abdominal	DEX and bupivacaine <i>i.t.</i> vs DEX and morphine and bupivacaine <i>i.t.</i> vs morphine and bupivacaine <i>i.t.</i>	RCT		Change in cellular immunity (CD3 ⁺ , CD4 ⁺ , CD8 ⁺ , CD16 ⁺ , CD56 ⁺), change in cytokines (IL-1 β , IL-6, IL-10, TNF)	1–2	Unknown	NCT03024957
Breast	DEX and bupivacaine in PECS block vs bupivacaine alone	RCT		Opioid consumption; pain; cortisol level	3	Unknown	NCT03046238
Colorectal	DEX (bolus then continuous) vs lidocaine <i>i.v.</i> (continuous) vs morphine <i>i.t.</i>	RCT	Recurrence	MMP-2, MMP-9, IL-6, VEGF Lymphocyte subset	NA	Recruiting	NCT05742438
Pituitary	DEX <i>i.v.</i> (bolus then continuous) vs placebo	RCT		Cortisol, ACTH Pain	4	Unknown	NCT02549768
Solid tumors	DEX <i>i.v.</i> (continuous) vs placebo	RCT	Recurrence	Inflammation (CRP, ESR, NLR, PLR, plasma viscosity, lactate) Opioid use	2–3	Not yet recruiting	NCT04106999
Solid tumors	DEX <i>i.v.</i> (continuous) vs placebo	RCT	RFS, OS, cancer-specific survival; event-free survival		NA	Active, not yet recruiting	NCT03012971
Solid tumors	DEX <i>i.v.</i> (bolus then continuous) vs placebo	RCT	PFS, OS, cancer-specific survival; event-free survival	Pain	NA	Recruiting	NCT06030804
Uterus	DEX <i>i.v.</i> (bolus then continuous) vs placebo	RCT		ACTH	3	Unknown	NCT03524950

Abbreviations: ACTH, adrenocorticotropic hormone; DEX, dexmedetomidine; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; *i.t.*, intrathecal; *i.v.*, intravenous; MMP, matrix metalloproteinase; NA, non-applicable; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PECS, pectoralis; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; RCT, randomized controlled trial; RFS, recurrence-free survival; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

the peripheral blood such as CRP, erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), plasma viscosity and lactate on postoperative day 5. Three trials are exploring the surgical glucocorticoid stress generated by inflammatory pain during breast, pituitary, and uterine surgery (NCT02549768; NCT03524950; NCT03046238). These trials assess the plasma level of ACTH and cortisol prior and after the surgery and hypothesize that the intravenous DEX alone or DEX co-injected with the local anesthetic bupivacaine in pectoralis block might decrease the surgery-induced immunosuppressive stress. Moreover, the phase 1–2 NCT03024957 study investigates whether the combinations of DEX and

bupivacaine or DEX and morphine injected through spinal anesthesia induces changes in cellular immunity and protumor inflammatory cytokine release immediately after and 1 day after surgery compared to the classically used association morphine and bupivacaine (Table 5). Of note, one retrospective study and two RCTs are evaluating whether DEX employed in an opioid-free anesthesia (OFA) protocol during primary solid tumor resection can minimize the secretion of circulating protumor factors, alleviate inflammatory and glucocorticoid stress, reduce the occurrence of relapses, and improve survival after surgery compared to the control groups receiving general anesthesia comprising opioids (NCT05448586; NCT04529135; NCT05172739) (Table 6).

Table 6. Completed and ongoing trials investigating the role of OFA on cancer outcome.

Tumor type	Design	OFA protocol	Study type	Oncological endpoints	Potential endpoints related to cancer outcome	Phase	NCT number
Breast Cervix Endometrial Ovarian	OFA vs standard GA (with opioids)	Dexmedetomidine +ketamine +lidocaine +propofol	Retrospective	Recurrence at 12 months Survival at 12 months	Postoperative Systemic Inflammatory Response (CRP, WBC, platelets)	NA	NCT05448586
Gastric	OFA vs standard GA (with opioids)	Dexmedetomidine +propofol	RCT	Readmission rate at 3 months	Pain, analgesic requirement	NA	NCT04529135
Lung	OFA vs standard GA (with opioids)	Dexmedetomidine +hyoscine +ketamine +lidocaine +midazolam +pregabalin +propofol	RCT		Inflammation (LMR, NLR, PLR); surgical stress response (IL-1, IL-6, IL-8, IL-10, TNF- α , CRP, WBC, AVP, cortisol, HIF-1 α , VEGF, NF- kB); pain	4	NCT05172739

Abbreviations: AVP, arginine-vasopressin; CRP, C-reactive protein; GA, general anesthesia; HIF, hypoxia-inducible factor; IL, interleukin; LMR, lymphocyte-to-monocyte ratio; NA, non-applicable; NK-kB, nuclear factor kappa B; NLR, neutrophil-to-lymphocyte ratio; OFA, opioid-free anesthesia; OS, overall survival; PLR, platelets-to-lymphocyte ratio; RCT, randomized controlled trial; RFS, recurrence-free survival; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; WBC, white blood cell.

Some of these studies have protocols designed to mimic clinical practice by combining DEX with anti-tumor anesthetics such as lidocaine while avoiding the administration of opioids. Altogether, ongoing trials will yield additional data on the question whether the use of DEX could improve oncological outcomes by decreasing the incidence of recurrences.

Discussion

Previous basic research indicates that many analgesic agents used in clinical practice, such as local anesthetics, intravenous hypnotics or beta-blockers, might positively influence oncological outcomes.^{82–84} Here, we compiled evidence suggesting that the α 2-AR agonist DEX, which is currently used in intensive and anesthetic care for its sedative and anxiolytic properties, exerts direct cytolytic effects on malignant cells and induces indirect anti-tumor immunity by reducing inflammatory pain with the consequent production of stress hormones and protumorigenic cytokines. Indeed, acute pain and inflammation favor oncogenesis by generating broad surgical stress responses. Nociception produced during the surgical resection of primary solid tumors, activates the surge of several stress hormones including ACTH, cortisol and catecholamines. ACTH decreases the synthesis of immunoglobulins, while cortisol and catecholamines alter the proliferation and activity of circulating leucocytes and negatively impact the infiltration of immune cells into the tumor micro-environment (TME).^{85,86} In addition, catecholamines directly stimulate the proliferation, invasiveness and survival of residual tumor cells by acting on α and β -ARs located on the plasma membrane surface of malignant cells, thus promoting the occurrence of secondary lesion in distant organs.^{87–95} DEX is well-known for efficiently decreasing stress responses and exerting immunoprotective effects.^{96,97} In rodent models of inflammation induced by injection of endotoxin, bone fracture or local pancreatic injury, DEX significantly reduced markers of inflammation such as IL-1 β , IL-6 and TNF- α . In these models, DEX optimally controlled pain *via* the stimulation of the cholinergic anti-inflammatory pathway as indicated by the absence of additional beneficial effects of vagotomy or co-injection with acetylcholine receptors antagonists.^{9–11} In addition, DEX was

described to minimize glucocorticoid stress by impairing the release of catecholamines and cortisol during major non-oncological surgeries^{98–100} leading to the hypothesis that DEX could promote similar effects during oncological procedures. In analogy to β -blockers, which mediate anti-tumor properties by directly acting on β -ARs expressed on malignant cells, DEX might interfere with procarcinogenic effects of epinephrine and norepinephrine acting on α -ARs on cancer cells.^{18,19,101–}

¹⁰⁴ Based on these premises, further investigations are exploring the potential anti-tumor property of DEX. As veterinarians currently use DEX for sedation and general anesthesia during surgical procedures in a large variety of animals, the pharmacodynamics and pharmacokinetics of DEX are relatively well known, allowing impactful studies in rodent models. First *in vitro* and *in vivo* studies reported paradoxical results in thus far that DEX induced concentration-dependent and cell type-specific effects that often were divergent with respect to their oncological outcome.^{22,29} Nevertheless, when employed at clinically relevant concentrations through continuous infusion, DEX tends to promote antineoplastic effects and hence impairs the proliferation, invasiveness and survival of malignant cells.^{27–39,43,44} In addition, treatment of distinct types of tumors with DEX significantly limited inflammasome activation, thus decreasing the secretion of IL-1 β that is mostly considered as a protumorigenic cytokine.^{105–107} Altogether, DEX alters the secretion of protumor inflammatory cytokines and alleviates surgical glucocorticoid stress, thus reducing tumor growth and limiting the spread of circulating tumor cells to distant organs. Published clinical research also revealed that DEX slows or halts surgery-induced immunosuppression.^{53,55,56,58,61–70,72,75,78,79}

However, most studies reported a relatively moderate decrease in CD4⁺ T cells in DEX treated patients (as compared to CTLs), though did not investigate the true phenotype of CD4⁺ T cells, which also includes immunosuppressive regulatory T cells (Tregs). Two meta-analyses indicated that DEX administered during cancer surgery reduced the secretion of protumorigenic inflammatory cytokines such as IL-6 and TNF- α but increased the levels of circulating T cells. It should be noted that not all included RCTs have investigated DEX-mediated immunomodulation and its consequences on immunosurveillance^{59,60} (Figure 4). Very few RCTs aimed to evaluate the impact of

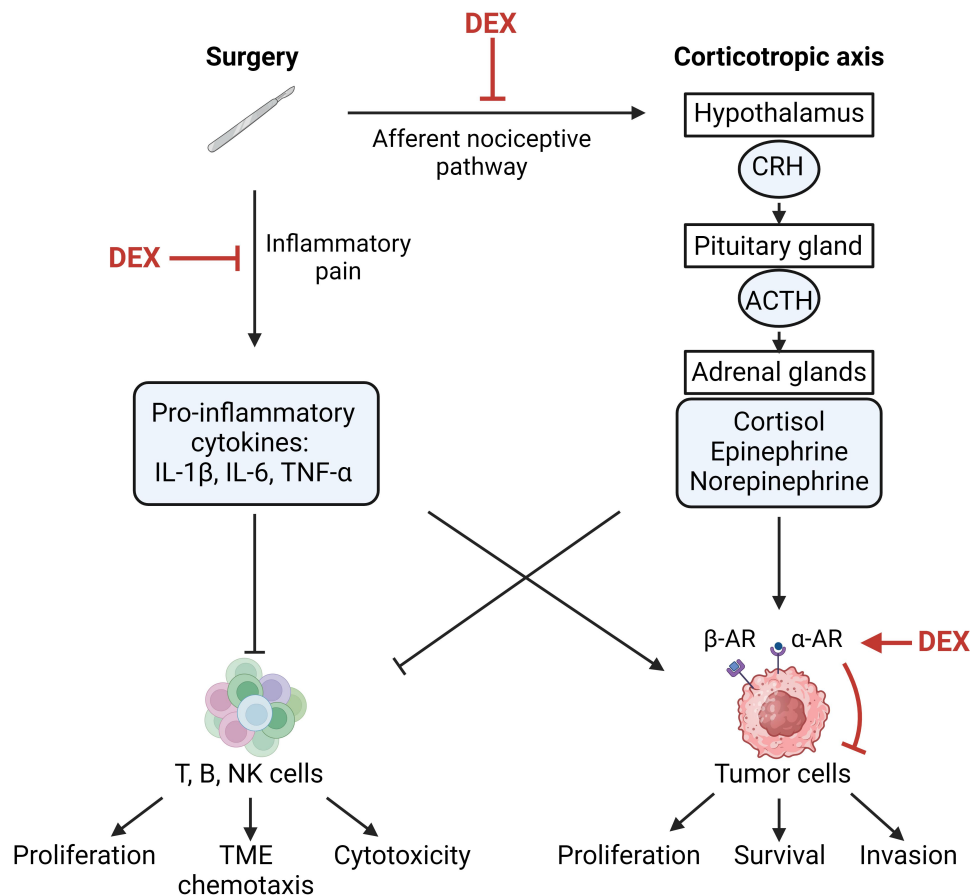


Figure 4. Scheme of central and peripheral actions of dexmedetomidine. Surgery-induced inflammatory pain activates the corticotropic axis *via* the stimulation of afferent nociceptive pathways and promotes local production of protumor cytokines such as IL-1 β , IL-6 and TNF- α . The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates the synthesis of adrenocorticotropic hormone (ACTH) by the pituitary gland. In response to ACTH, adrenal glands release cortisol and catecholamines (epinephrine and norepinephrine) into the systemic circulation. Catecholamines, potentiated by tumorigenic cytokines, act on α - and β -adrenoceptors (α -AR, β -AR) located on the surface of tumor cells to enhance their proliferation, survival and migration. These protumor molecules inhibit the chemotaxis and cytotoxicity of the immune effectors (T, B, NK cells) in the tumor bed and its microenvironment (TME). Dexmedetomidine (DEX) could alleviate both corticotropic axis activity and the release of protumor cytokines by optimally controlling inflammatory pain. Through its agonist effect on α -adrenoceptor, DEX might also impair the malignant properties of tumor cells directly. Created with <https://www.BioRender.com>

DEX on recurrence-free survival or overall survival, yielding mostly inconclusive results. These studies were either retrospective, suffered from a lack of inclusions or were affected by confounding factors such as procedures afflicted by high morbidity and mortality.⁵⁰ In addition, the study of Cata *et al.* involved important confusion biases such as aged patients with aggressive types of tumors and co-morbidities (ASA 3–4).⁵⁰ Moreover, among the completed or ongoing studies evaluating the survival, NCT03370588 and NCT04106999 are including patients undergoing HIPEC surgery, which is a major procedure associated with high morbidity (22–50%) and mortality (2–5%), rendering difficult the interpretation of the results.¹⁰⁸ Similarly, the trial NCT02739958 is enrolling patients operated for total laryngectomy, which is one of the most painful and inflammatory otorhinolaryngological procedures. None of these studies evaluated the possibility of synergistic effects of DEX associated with other agents.^{109–113} Interestingly, three ongoing trials are investigating the benefits of DEX combined with the local anesthetic, bupivacaine, administered through intrathecal, loco-regional or local injection, on the decrease in inflammatory stress markers and protumor factors such as MMP-2, MMP-9

and VEGF. Finally, three ongoing clinical trials focus on the OFA protocol combining DEX with local anesthetics, ketamine, magnesium, and propofol to reduce or avoid the requirement of opioid during surgery. Ample preclinical and clinical evidence indicates that local anesthetics and propofol mediate anti-tumor activity whereas opioids rather stimulate oncogenesis. Thus, OFA offers a possibility to potentiate the anticancer effects of DEX, while avoiding the use of protumorigenic agents. Of note, no clinical study using DEX with intravenous loading dose and continuous infusion, noticed severe side effects such as bradycardia or hypotension, which would have led to the termination of the trial. In sum, DEX appears as a safe and promising perioperative antitumor agent. Further data are expected to definitively prove the capacity of DEX to sustain anticancer immunity and to improve disease outcome after cancer surgery.

Conclusion

Accumulating preclinical and clinical evidence suggests that dexmedetomidine (DEX) exhibits anti-tumor effects, by directly acting on malignant cells to halt proliferation, invasion and survival,

while indirectly reducing inflammatory stress responses produced by the surgical procedure, thus stimulating anticancer immunity. We must deplore the absence of prospective randomized trials investigating the impact of the administration of DEX on recurrence-free and overall survival, which would allow to recommend the broad clinical application of DEX in onco-anesthesia. Furthermore, we believe that additional trials should confirm the utility of DEX in opioid-free-anesthesia protocols that combine several anesthetic agents such as local anesthetics for the avoidance or reduction of adverse opioid effects as well as improved oncological outcome. Future clinical investigations will need to confirm such DEX-mediated anticancer effects.

Abbreviations

Ach	Acetylcholine
AChE	Acetylcholinesterase
aHSC	Activated hepatic stellate cells
AR	Adrenoceptor
ASC	Adapter protein apoptosis speck-like protein containing a CARD
AVP	Arginine-vasopressin
CI	Confidence interval
CPT1A	Carnitine palmitoyltransferase 1A
DC	Dendritic cell
DEX	Dexmedetomidine
EGFR	Epidermal growth factor receptor
ENT	Ear-Nose-Throat
ERK	Extracellular regulated kinase
ESR	Erythrocyte sedimentation rate
GA	General anesthesia
GABA	Gamma-aminobutyric acid
HCC	Hepatocellular carcinoma
HIF	Hypoxia-inducible factor
HIPEC	Hyperthermic intraperitoneal chemotherapy
HMGA2	High mobility group AT-hook 2
HR	Hazard ratio
IFN	Interferon
IGF	Insulin-like growth factor
IL	Interleukin
IRS1	Insulin receptor substrate 1
IV	Intravenous
LMR	lymphocyte-to-monocyte ratio
MALAT1	Metastasis associated lung adenocarcinoma transcript 1
MMP	Matrix metalloproteinase
NETs	Neutrophil extracellular traps
NK	Natural killer
NF-Kb	Nuclear factor kappa B
NLR	neutrophil-to-lymphocyte ratio
NLRP3	NOD-like receptor family pyrin domain containing 3
OFA	Opioid-free-anesthesia
OGD	Oxygen-glucose deprivation
OS	overall survival
PI3K/Akt	Phosphoinositide 3 kinase/Protein kinase B
PLR	platelet-to-lymphocyte ratio
RFS	Recurrence-free survival
ROS	Reactive oxygen species
SOX9	Sry (Sex determining region Y)-box 9
STAT3	Signal transducer and activator of transcription 3
TMPRSS2	Transmembrane protease serine 2
TNF	Tumor necrosis factor
TXNIP	Thioredoxin (TRX)-interacting protein
VEGF	Vascular endothelial growth factor
VLPN	Ventrolateral preoptic nucleus
WBC	White blood cells

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