**APPENDIX A. STUDY GRADING TABLES**

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| SECTION: **Surgical Stress Response and Cancer Recurrence** | | | |
|  | **AUTHOR** | **ANIMAL OR CELL** | **GRADE** |
|  | Piegeler | Cell | Strong |
|  | Piegeler | Cell | Strong |
|  | Iliopoulis | Cell | Strong |
|  | Sodeur | Animal | Average |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | | |
|  | SECTION:  **Analgesic techniques and influence on immunomodulation and immune cell function** | | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** | |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | | |
|  | Tie J, Wang Y et al: Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Sci Transl Med 2016; 8: 346ra92 | 1 | 1 | 2 | 2 | | **6** | P-cohort | | WEAK FOR NOT USING |
|  | Koltun WA, Bloomer MM, Tilberg AF, Seaton JF, Ilahi O, Rung G, Gifford RM, Kauffman GL, Jr.: Awake epidural anesthesia is associated with improved natural killer cell cytotoxicity and a reduced stress response. Am J Surg 1996; 171: 68-72; discussion 72-3 | 0 | 2 | 2 | 3 | | **7** | P-cohort  Humans | | WEAK FOR USING |
|  | Koda K, Saito N, Takiguchi N, Oda K, Nunomura M, Nakajima N: Preoperative natural killer cell activity: Correlation with distant metastases in curatively research colorectal carcinomas. International Surgery 1997; 82: 190-193 | -3 | 2 | 2 | 2 | | **3** | Prospect  Humans | | STRONG FOR NOT USING |
|  | Fujisawa T, Yamaguchi Y: Autologous tumor killing activity as a prognostic factor in primary resected nonsmall cell carcinoma of the lung. Cancer 1997; 79: 474-81 | -4 | 2 | 2 | 2 | | **2** | Prospect  Humans | | STRONG FOR NOT USING |
|  | Yeager MP, Procopio MA, DeLeo JA, Arruda JL, Hildebrandt L, Howell AL: Intravenous fentanyl increases natural killer cell cytotoxicity and circulating CD16(+) lymphocytes in humans. Anesth Analg 2002; 94: 94-9, table of contents | 1 | 2 | 2 | 2 | | **7** | P. Cohort  Humans | | WEAK FOR USING |
|  | Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE: The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. Anesth Analg 2000; 90: 1411-4 | -3 | 2 | 2 | 2 | | **3** | P- cohort  Humans | | STRONG FOR NOT USING |
|  | Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, Kavanagh BP, Buggy DJ: Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg Anesth Pain Med 2010; 35: 490-5 | 2 | 2 | 2 | 3 | | **9** | Prospect  Random  Humans | | STRONG FOR USING |
|  | Wang XT, Lv M, Guo HY: Effects of epidural block combined with general anesthesia on antitumor characteristics of T helper cells in hepatocellular carcinoma patients. J Biol Regul Homeost Agents 2016; 30: 67-77 | 3 | 2 | 2 | 3 | | **10** | Prospect  Humans | | STRONG FOR USING |
|  | Dong H, Zhang Y, Xi H: The Effects of Epidural Anaesthesia and Analgesia on Natural Killer Cell Cytotoxicity and Cytokine Response in Patients with Epithelial Ovarian Cancer Undergoing Radical Resection. Journal of International Medical Research 2012; 40: 1822-1829 | 3 | 2 | 2 | 3 | | **10** | Prospect  Humans | | STRONG FOR USING |
|  | Li JM, Shao JL, Zeng WJ, Liang RB: General/epidural anesthesia in combination preserves NK cell activity and affects cytokine response in cervical carcinoma patients undergoing radical resection: a cohort prospective study. Eur J Gynaecol Oncol 2015; 36: 703-7 | 2 | 2 | 2 | 3 | | **9** | Prospect  Humans | | STRONG FOR USING |
|  | Purdy M, Kokki M, Anttila M, Aspinen S, Juvonen P, Korhonen R, Selander T, Kokki H, Eskelinen M: Does the Rectus Sheath Block Analgesia Reduce the Inflammatory Response Biomarkers' IL-1ra, IL-6, IL-8, IL-10 and IL-1beta Concentrations Following Surgery? A Randomized Clinical Trial of Patients with Cancer and Benign Disease. Anticancer Res 2016; 36: 3005-11 | -3 | 2 | 2 | 2 | | **3** | Prospect  Human | | STRONG FOR NOT USING |
|  | Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H: The Effect of Perioperative Intravenous Lidocaine on Postoperative Pain and Immune Function. Anesthesia and Analgesia 2009; 109: 1464-1469 | 2 | 2 | 2 | 3 | | **9** | Prospect  Humans | | STRONG FOR USING |
|  | Beilin B, Rusabrov Y, Shapira Y, Roytblat L, Greemberg L, Yardeni IZ, Bessler H: Low-dose ketamine affects immune responses in humans during the early postoperative period. British Journal of Anaesthesia 2007; 99: 522-527 | 0 | 2 | 2 | 2 | | **6** | Prospect  Humans | | WEAK FOR NOT USING |

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| SECTION: **Analgesic techniques and influence on immunomodulation and immune cell function** | | | |
| **REF #** | **AUTHOR** | **ANIMAL OR CELL** | **GRADE** |
|  | Kim SY, Kang JW, Song X, Kim BK, Yoo YD, Kwon YT, Lee YJ: Role of the IL-6-JAK1-STAT3-Oct-4 pathway in the conversion of non-stem cancer cells into cancer stem-like cells. Cell Signal 2013; 25: 961- | Cell Study/Xenograft | Average |
|  | Pollock RE, Lotzova E: Surgical-stress-related suppression of natural killer cell activity: a possible role in tumor metastasis. Nat Immun Cell Growth Regul 1987; 6: 269-78 | In Vivo Animal | Average |
|  | Pollock RE, Lotzova E, Stanford SD, Romsdahl MM: Effect of surgical stress on murine natural killer cell cytotoxicity. J Immunol 1987; 138: 171-8 | In Vivo Animal | Average |
|  | Page GG, Blakely WP, Ben-Eliyahu S: Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001; 90: 191-9 | In Vivo Animal | Strong |
|  | Shavit Y, Martin FC, Yirmiya R, Ben-Eliyahu S, Terman GW, Weiner H, Gale RP, Liebeskind JC: Effects of a single administration of morphine or footshock stress on natural killer cell cytotoxicity. Brain Behav Immun 1987; 1: 318-28 | In Vivo In Animal | Average |
|  | Shavit Y, Terman GW, Lewis JW, Zane CJ, Gale RP, Liebeskind JC: Effects of footshock stress and morphine on natural killer lymphocytes in rats: studies of tolerance and cross-tolerance. Brain Res 1986; 372: 382-5 | In Vivo Animal | Average |
|  | Sood AK, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, Li Y, Gershenson DM, Lutgendorf S, Cole SW: Stress hormone-mediated invasion of ovarian cancer cells. Clin Cancer Res 2006; 12: 369-75 | Cell Study | Average |
|  | Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, Barsky SH, Glaser R: Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav Immun 2009; 23: 267-75 | Cell Study | Average |
|  | Franchi S, Panerai AE, Sacerdote P: Buprenorphine ameliorates the effect of surgery on hypothalamus-pituitary-adrenal axis, natural killer cell activity and metastatic colonization in rats in comparison with morphine or fentanyl treatment. Brain Behav Immun 2007; 21: 767-74 | In Vivo Animal | Strong |
|  | Wada H, Seki S, Takahashi T, Kawarabayashi N, Higuchi H, Habu Y, Sugahara S, Kazama T: Combined spinal and general anesthesia attenuates liver metastasis by preserving TH1/TH2 cytokine balance. Anesthesiology 2007; 106: 499-506 | In Vivo Animal | Strong |
|  | Ramirez MF, Tran P, Cata JP: The effect of clinically therapeutic plasma concentrations of lidocaine on natural killer cell cytotoxicity. Reg Anesth Pain Med 2015; 40: 43-8 | Cell Study | Average |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: Opioids and Cancer | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | Yokota T, Uehara K, Nomoto Y. Intrathecal morphine suppresses NK cell activity following abdominal surgery. Can J Anaesth 2000;47:303-8. Grade: 6 | 3 | 1 | 0 | 2 | | **6** |  |  |
|  | Tabellini G, Borsani E, Benassi M, et al. Effects of opioid therapy on human natural killer cells. Int Immunopharmacol 2014;18:169-74. Grade: 6 |  |  |  |  | | **6** |  |  |
|  | Yeager MP, Colacchio TA, Yu CT, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology 1995;83:500-8. Grade 6 |  |  |  |  | | **6** |  |  |

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| --- | --- | --- | --- |
| SECTION: **Opioids and Cancer** | | | |
|  | **AUTHOR** | **ANIMAL OR CELL** | **GRADE** |
|  | Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001;90:191-9.Grade: strong | ANIMAL | STRONG |
|  | Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012;116:940-5. Grade: average | REVIEW | AVERAGE |
|  | Gach K, Wyrebska A, Fichna J, Janecka A. The role of morphine in regulation of cancer cell growth. Naunyn Schmiedebergs Arch Pharmacol 2011;384:221-30. Grade: weak | CELL | WEAK |
|  | Borner C, Stumm R, Hollt V, Kraus J. Comparative analysis of mu-opioid receptor expression in immune and neuronal cells. J Neuroimmunol 2007;188:56-63. Grade: weak | CELL | WEAK |
|  | Kraus J. Regulation of mu-opioid receptors by cytokines. Front Biosci (Schol Ed) 2009;1:164-70. Grade: weak | CELL | WEAK |
|  | Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010;105:106-15. Grade: weak | REVIEW | WEAK |
|  | Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: a structure-related activity study. Br J Pharmacol 1997;121:834-40. Grade: average | ANIMAL | AVERAGE |
|  | Bonnet MP, Beloeil H, Benhamou D, Mazoit JX, Asehnoune K. The mu opioid receptor mediates morphine-induced tumor necrosis factor and interleukin-6 inhibition in toll-like receptor 2-stimulated monocytes. Anesth Analg 2008;106:1142-9. Grade: average | CELL | AVERAGE |
|  | Roy S, Wang J, Charboneau R, Loh HH, Barke RA. Morphine induces CD4+ T cell IL-4 expression through an adenylyl cyclase mechanism independent of the protein kinase A pathway. J Immunol 2005;175:6361-7. Grade: average | CELL | AVERAGE |
|  | Borner C, Warnick B, Smida M, et al. Mechanisms of opioid-mediated inhibition of human T cell receptor signaling. J Immunol 2009;183:882-9. Grade: weak | CELL | WEAK |
|  | Scott M, Carr DJ. Morphine suppresses the alloantigen-driven CTL response in a dose-dependent and naltrexone reversible manner. J Pharmacol Exp Ther 1996;278:980-8. Grade: average | CELL | AVERAGE |
|  | Zhang EY, Xiong J, Parker BL, et al. Depletion and recovery of lymphoid subsets following morphine administration. Br J Pharmacol 2011;164:1829-44. Grade: average | CELL | AVERAGE |
|  | Fuggetta MP, Di Francesco P, Falchetti R, et al. Effect of morphine on cell-mediated immune responses of human lymphocytes against allogeneic malignant cells. J Exp Clin Cancer Res 2005;24:255-63. Grade: weak | CELL | WEAK |
|  | Borman A, Ciepielewski Z, Wrona D, et al. Small doses of morphine can enhance NK cell cytotoxicity in pigs. Int Immunopharmacol 2009;9:277-83. Grade: strong | ANIMAL | STRONG |
|  | Madera-Salcedo IK, Cruz SL, Gonzalez-Espinosa C. Morphine decreases early peritoneal innate immunity responses in Swiss-Webster and C57BL6/J mice through the inhibition of mast cell TNF-alpha release. J Neuroimmunol 2011;232:101-7. Grade: strong | ANIMAL | STRONG |
|  | Nguyen J, Luk K, Vang D, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. Br J Anaesth 2014;113 Suppl 1:i4-13. Grade: strong | ANIMAL | STRONG |
|  | Simon RH, Arbo TE. Morphine increases metastatic tumor growth. Brain Res Bull 1986;16:363-7. Grade: average | ANIMAL | AVERAGE |
|  | Moon TD. The effect of opiates upon prostatic carcinoma cell growth. Biochem Biophys Res Commun 1988;153:722-7. Grade: average | CELL | AVERAGE |
|  | Ishikawa M, Tanno K, Kamo A, Takayanagi Y, Sasaki K. Enhancement of tumor growth by morphine and its possible mechanism in mice. Biol Pharm Bull 1993;16:762-6. Grade: average | ANIMAL | AVERAGE |
|  | Page GG, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. Pain 1993;54:21-8. Grade: weak | ANIMAL | WEAK |
|  | Lazarczyk M, Matyja E, Lipkowski AW. A comparative study of morphine stimulation and biphalin inhibition of human glioblastoma T98G cell proliferation in vitro. Peptides 2010;31:1606-12. Grade: average | CELL | AVERAGE |
|  | Tegeder I, Grosch S, Schmidtko A, et al. G protein-independent G1 cell cycle block and apoptosis with morphine in adenocarcinoma cells: involvement of p53 phosphorylation. Cancer Res 2003;63:1846-52. Grade: average | CELL | AVERAGE |
|  | Yeager MP, Colacchio TA. Effect of morphine on growth of metastatic colon cancer in vivo. Arch Surg 1991;126:454-6. Grade: average | ANIMAL | AVERAGE |
|  | Mathew B, Lennon FE, Siegler J, et al. The novel role of the mu opioid receptor in lung cancer progression: a laboratory investigation. Anesth Analg 2011;112:558-67.Grade: strong | CELL | STRONG |
|  | Afsharimani B, Doornebal CW, Cabot PJ, Hollmann MW, Parat MO. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. Br J Pharmacol 2015;172:251-9. Grade: strong | ANIMAL | STRONG |
|  | Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249-57. Grade: strong | REVIEW | STRONG |
|  | Hobbs SK, Monsky WL, Yuan F, et al. Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proc Natl Acad Sci U S A 1998;95:4607-12. Grade: average | CELL | AVERAGE |
|  | Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002;62:4491-8. Grade: strong | CELL | STRONG |
|  | Farooqui M, Geng ZH, Stephenson EJ, Zaveri N, Yee D, Gupta K. Naloxone acts as an antagonist of estrogen receptor activity in MCF-7 cells. Mol Cancer Ther 2006;5:611-20. Grade: average | CELL | AVERAGE |
|  | Singleton PA, Moss J. Effect of perioperative opioids on cancer recurrence: a hypothesis. Future Oncol 2010;6:1237-42. Grade: weak | CELL | WEAK |
|  | Stefano GB, Hartman A, Bilfinger TV, et al. Presence of the mu3 opiate receptor in endothelial cells. Coupling to nitric oxide production and vasodilation. J Biol Chem 1995;270:30290-3. Grade: weak | CELL | WEAK |
|  | Balasubramanian S, Ramakrishnan S, Charboneau R, Wang J, Barke RA, Roy S. Morphine sulfate inhibits hypoxia-induced vascular endothelial growth factor expression in endothelial cells and cardiac myocytes. J Mol Cell Cardiol 2001;33:2179-87. Grade: weak | CELL | WEAK |
|  | Koodie L, Ramakrishnan S, Roy S. Morphine suppresses tumor angiogenesis through a HIF-1alpha/p38MAPK pathway. Am J Pathol 2010;177:984-97. Grade: average | CELL | AVERAGE |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: NSAIDs and Cancer Recurrence | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | Giardiello FM. et al. N.Engl.J.Med.,328,1313-1316 | 6 | 2 | 2 | 2 | | **12** | RCT | Reduced number and size of colonic polyps w sulindac |
|  | Midgley RS et al J Clin Oncol. 2010 Oct 20;28(30):4575-80. | 6 | -1 | 2 | 2 | | **9** | RCT | No benefit of rofecoxib on Colorectal ca |
|  | Retsky M et al. . Curr Med Chem. 2013 Nov; 20(33): 4163–4176. | 1 | 2 | 2 | 2 | | **7** | Retrospective. Not randomised | Reduced early recurrence of breast cancer w NSAIDs |
|  | Muscat JE. Et al. Cancer. 2003;97(7):1732-1736 | 1 | 1 | 0 | 1 | | **3** | Case Control | NSAIDs were protective vs lung cancer in smokers |
|  | Schreinemachers DM et al Epidemiology. 1994;5:138-146 | 1 | 2 | 2 | 2 | | **7** | Observational | Aspirin decreases risk of multiple cancers |
|  | Harris RE et al . International Journal of Biological Sciences 2007;3(5):328-334. | 1 | 2 | 2 | 2 | | **7** | Case Control | COX2 inhibitors decrease risk of developing breast cancer |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: Ketamine and Cancer Recurrence | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | Beilin B, et al. Br J Anaesth 2007;99:522-7 | 3 | 1 | 0 | 1 | | **5** | RA | RCT trial evaluates the cytokine expression by ketamine infusion. |

**Animal Studies (Ketamine):**

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| Forget at al. *Eur J Anaesthesiol* 2010;27:233-40 | **Strong** evidence, although the murine model may limit extrapolation to humans. |
| DeClue AE, et al. *American Journal of Veterinary Research* 2008;69:228-232. | **Strong** evidence but unfortunately evaluates effects of ketamine on TNF –alpha, but it was not evaluated in cancer model, therefore, does not answer the main question posted in manuscript. |

**CELL STUDIES (Ketamine):**

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| Li CY et al. Can J Anaesth. 1997;4(9):989-95 | **STRONG:** Quality of the study is average as is done in murine model with appropriate study design, significant dose response findings and consistency of effects. |
| Nishina K, et al. Anesth Analg. 1998;86(1):159-65 | **STRONG:** Ketamine in human cell lines showed positive effects on neutrophil funcion when compared with other commonly used IV anesthetics. |
| Shimaoka et al. Br J Anaesth 1996;77(2):238-42). | **STRONG** quality, the main limitation refers to the murine model. |
| Fujimoto T., *Anesth Analg* 2005;101:1054-9. | **STRONG** quality except for the use of canine cell line. |

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| **SECTION: LOCAL ANESTHETICS & CANCER RECURRENCE** | | |
| **AUTHOR** | **ANIMAL OR CELL** | **GRADE** |
| Stasinopuolis | Cell | Average |
| Ness | Animal | Average |
| Schreiner | Cell | Average |
| Stewart | Cell | Weak |
| Macgregor | Animal | Strong |
| Schmidt | Animal | Strong |
| Azuma | Cell | Moderate |
| Blumenthal | Animal and Cell | Strong |
| Hammer | Cell | Average |
| Lan | Cell | Average |
| Goel | Cell | Weak |
| Flynn | Cell | Weak |
| Sinclair | Cell | Average |
| Tanelian | Cell | Strong |
| Brackenburg | Cell | Average |
| Lucchinetti | Cell | Strong |
| Fedder | Cell | Average |
| Lirk | Cell | Strong |
| Castellano | Cell | Average |
| Hollmann | Cell | Average |
| Piegeler | Cell | Strong |
| Xu | Cell | Average |
| Jiang | Cell | Average |
| Tada | Cell | Strong |
| Wang | Cell | Average |
| Chang | Cell | average |
| Johnson | Animal | Strong |
| Lang | Cell | Strong |
| Bar-yosef | Animal | Strong |
| Melamed | Animal | average |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: Alpha-2 Agonists and Cancer Recurrence | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | Memis D,et al. . *Br J Anaesth* 2007;98:550-2. | 3 | 1 | 0 | 1 | | **5** | RA | RCT trial evaluates the cytokine expression by Dexmedetomidine, but inot in a population of cancer patients infusion. |

**Animal studies (Alpha-2- agonist):**

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| --- | --- |
| Xu Y, Zhang R, Li C et al. *Fundam Clin Pharmacol* 2015;29:462-71. | **Average.** Study is done for acute lung injury. There was no randomization |

**Cell studies (Alpha-2-agonists):**

|  |  |
| --- | --- |
| Xia M, Ji NN, Duan ML et al.. *Eur Rev Med Pharmacol Sci* 2016;20:3500-6. | **Strong** |
| Zhang X, Wang J, Qian W et al.. *Inflammation* 2014;37:942-9. | **Strong** |
| Peng M, Wang YL, Wang CY, Chen C.. *J Surg Res* 2013;179:e219-25 | **Strong** |
| Bruzzone A, Pinero CP, Castillo LF et al. *British journal of pharmacology* 2008;155:494-504 | **Strong** |
| Lai YC, Tsai PS, Huang CJ. *J Surg Res* 2009;154:212-9 | **Average** |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: Dexamethasone and Cancer Recurrence | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | Singh PP et al [Br J Anaesth.](https://www.ncbi.nlm.nih.gov/pubmed/24583820) 2014 Jul;113 Suppl 1:i68-73. | 4 | -1 | 2 | 1 | | **6** | RCT | Higher rate of distant mets with dexamethasone following colectomy |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | |
|  | SECTION: Perioperative Regional Anaesthesia and Cancer Recurrence | | | | | | | | |
|  | **Publication** | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | **Total** | **Type** | **Summary** |
|  | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | 13 max |  | |
|  | [Exadaktylos AK](http://www.ncbi.nlm.nih.gov/pubmed/?term=Exadaktylos%2520AK%255BAuthor%255D&cauthor=true&cauthor_uid=17006061) et al Anesthesiology. 2006 Oct;105(4):660-4. | 3 | 1 | 2 | 2 | | **8** | Follow up analysis of RCT | Paravertebral block at time of resections reduced breast cancer recurrence |
|  | Biki et al Anesthesiology 2008; 109: 180–7. | 3 | 1 | 2 | 2 | | **8** | Follow up analysis of RCT | Epidural reduced biochemiocal recurrence of prostate ca |
|  | Hiller JG et al [Acta Anaesthesiol Scand.](https://www.ncbi.nlm.nih.gov/pubmed/?term=hiller+hacking+link) 2014 Mar;58(3):281-90 | 1 | 1 | 0 | 1 | | **3** | Retrospective | Improved medium term survival and recurrence with epidural for oesophageal surgery. |
|  | Lacassie et al [Anesth Analg.](http://www.ncbi.nlm.nih.gov/pubmed/23868889) 2013 Sep;117(3):653-60. | 1 | -1 | 2 | 2 | | **4** | Retrospective analysis of register | No benefit of neuraxial anaesthesia for ovarian tumours |

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|  | **GRADE Evidence Ranking Worksheet** | | | | | | | | | | | | |
|  | SECTION: Neuraxial Analgesia | | | | | | | | | | | | RECOMMENDATION |
|  | **Publication** | | **Proof level** | **Risk Benefit ratio** | **Directness** | | **Critical or Important** | | **Total** | **Type** | | **Summary** |  |
|  | | | +6 to -7 | +2 to -1 | +2 or 0 | | +3 to +1 | | 13 max |  | | |  |
|  | Dong H, et al *J Int Med Res* 2012;40:1822-1829 | | 3 | 1 | 2 | | 2 | | **8** | RCT | | Protective effects of epidural anaesthesia on natural killer cell activity and cytokine response | WEAK FOR USING |
|  | Li JM, *Eur J Gynaecol Oncol* 2015;36:703-7. | | 3 | 1 | 2 | | 2 | | **8** | RCT | | Protective effect of epidural analgesia on natural killer cell function and IL-2. Also, EA showed anti-inflammatory effects | WEAK FOR USING |
|  | Fares KM, et al *Pain Physician* 2014;17:305-15. | | 3 | 1 | 1 | | 2 | | **7** | RCT | | Protective effects of epidural anaesthesia on cytokine response | WEAK FOR USING |
|  | Kun L, et al *Hepatogastroenterology* 2014;61:1142-7. | | 3 | 0 | 2 | | 2 | | **7** | RCT | | Effect of anesthetic technique on NK cell activity and cytokine response | WEAK FOR USING |
|  | Fant F, et al. *Br J Anaesth* 2013;110:747-57 | 3 | | 1 | 2 | 2 | | **8** | | | RCT | No protective effects of epidural anaesthesia on cytokine response except for IL-17 | WEAK FOR USING |

**Cell Studies (Neuraxial):**

|  |  |  |
| --- | --- | --- |
| SECTION: **Neuraxial Techniques & Cancer Recurrence** | | |
| **AUTHOR** | **ANIMAL OR CELL** | **GRADE** |
| Li Y, 2011. Effects of IL-17A on the occurrence of lung adenocarcinoma. | CELL | AVERAGE |
| Eiro N. 2017. Stromal factors involved in human prostate cancer development, progression and castration resistance. | CELL | AVERAGE |