Benefits of Regional Anesthesia in Cancer Surgery

Dominika Lipowska James, MD
Associate Professor of Anesthesiology
UNC Pain Fellowship. Director
Department of Anesthesiology
University of North Carolina, Chapel Hill, USA

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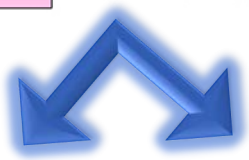
Objectives

- Discuss effects of perioperative stress on cellular function and cancer outcomes
- Describe effects of general anesthesia on cancer outcomes
- Discuss the effects of neuraxial analgesia on cancer recurrence and mortality as pertaining to various malignancies

2

Cancer Therapy

Treatment category	Specific treatments
Surgery Surgeon	• Lumpectomy • Lymph node dissection (seminal and axillary) • Mastectomy
Radiation therapy Radiation Oncologist	• External beam (3D conformal, IMRT) • Brachytherapy (High dose [HDR] or low dose [LDR]) • Intraoperative radiation (IORT)
Systematic therapy Medical Oncologist (attack cancer cells throughout the body)	• Chemotherapy • Hormone therapy • Targeted drug therapy



Cancer Remission

Cancer Recurrence
Death

Adopted from jeffreysterlingmd..com

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3

Cancer Treatment

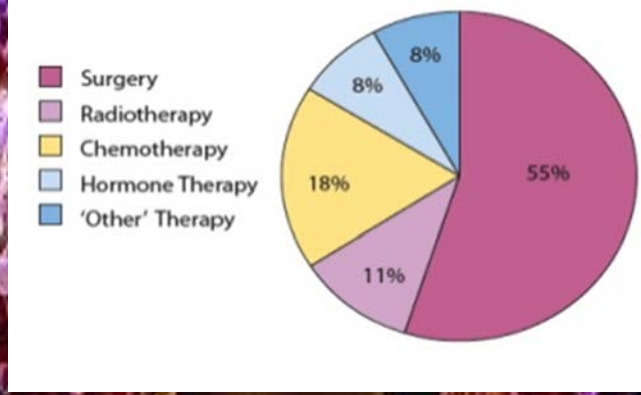
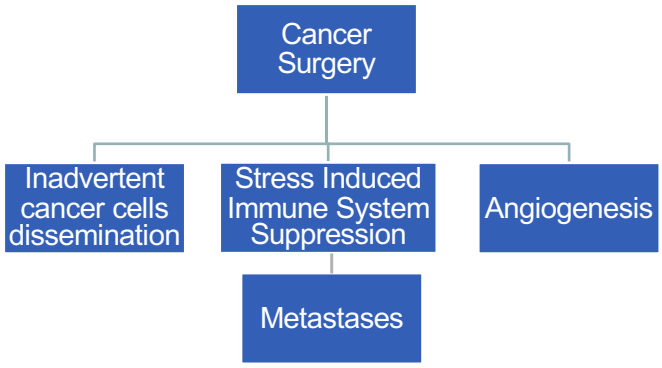


Image adopted from slideshare.com

4

Effects of Surgery on Cancer Outcomes



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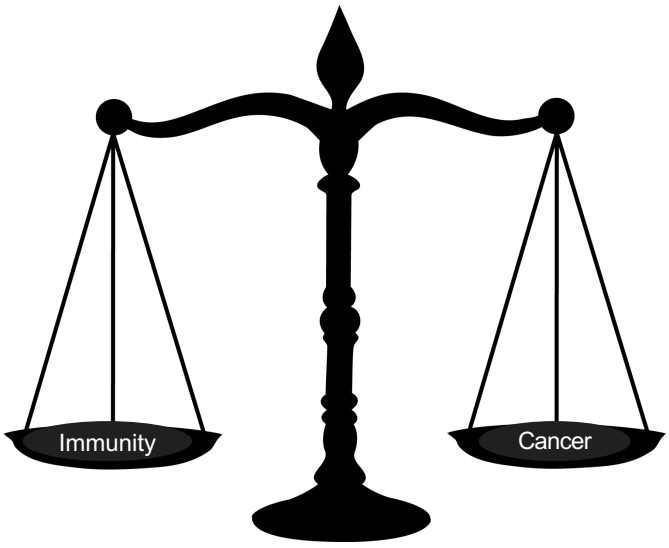
Constant Battle



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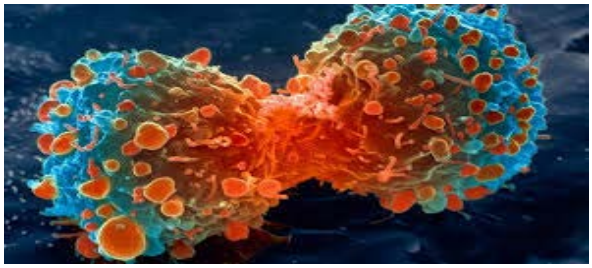
Why is cancer so tough to kill?



- Ability to evade immune surveillance
- Endless potential to replicate
- Resistance to apoptosis
- Micro- and macro-metastasis
- Angiogenesis

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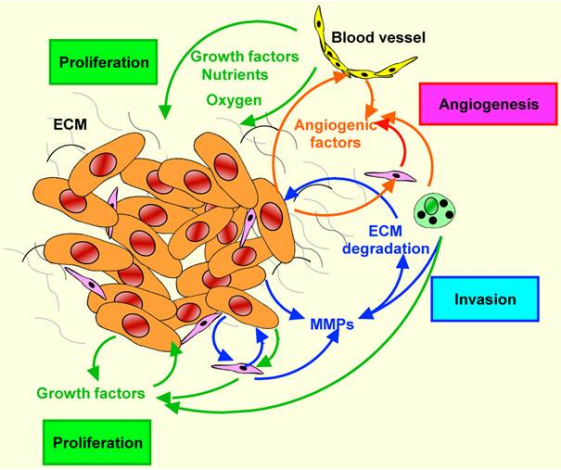
Tumor Microenvironment



1) Koontongkaew S. The Tumor Microenvironment Contribution to Development, Growth, Invasion and Metastasis of Head and Neck Squamous Cell Carcinomas. *J Cancer* 2013; 4(1):66-83. doi:10.7150/jca.5112. Available from http://www.jcancer.org/v04p0066.htm

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8

Function of the Immune System in Cancer Detection

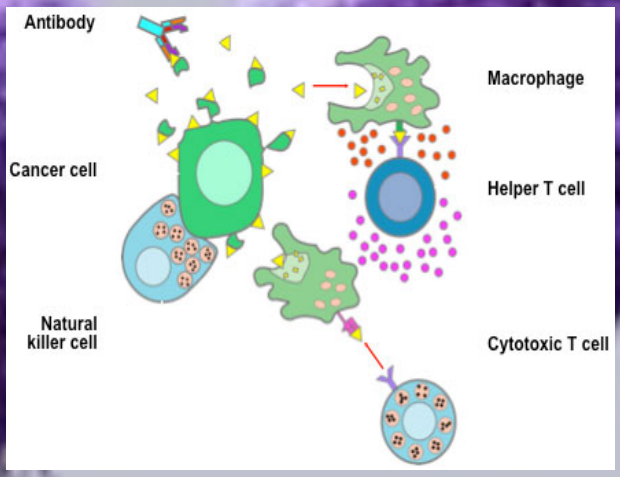

Image adopted from National Cancer Institute

9

Immunity and Cancer

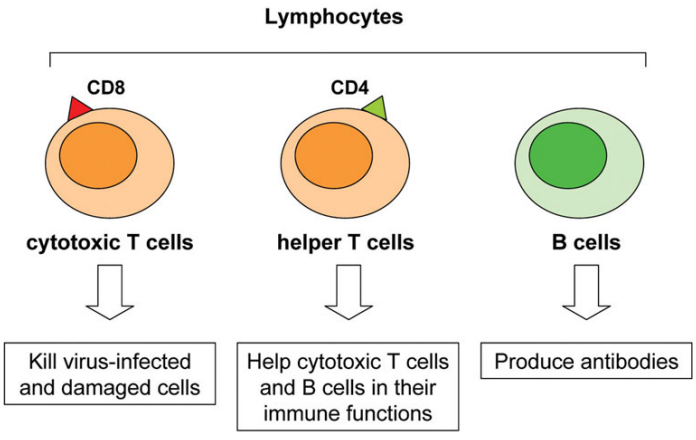

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Image adopted from http://www.open.ac.uk

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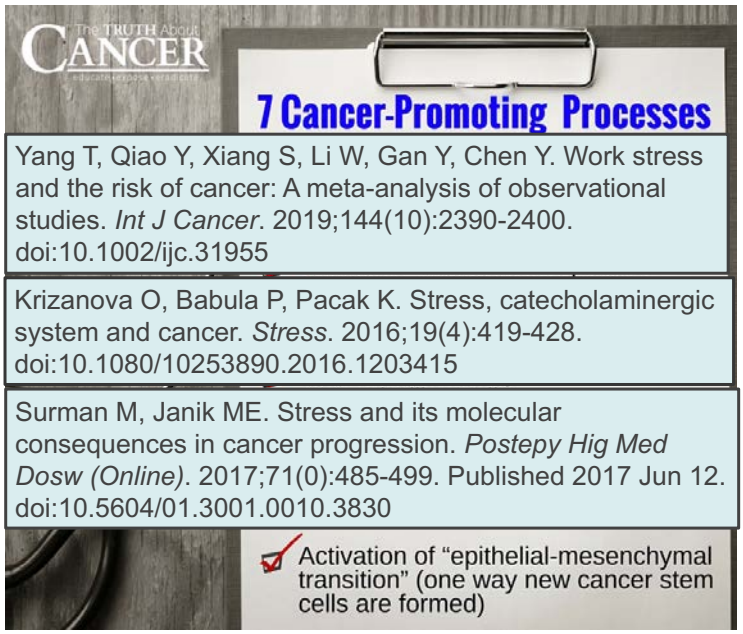
The TRUTH About CANCER
7 Cancer-Promoting Processes
Yang T, Qiao Y, Xiang S, Li W, Gan Y, Chen Y. Work stress and the risk of cancer: A meta-analysis of observational studies. *Int J Cancer*. 2019;144(10):2390-2400. doi:10.1002/ijc.31955
Krizanova O, Babula P, Pacak K. Stress, catecholaminergic system and cancer. *Stress*. 2016;19(4):419-428. doi:10.1080/10253890.2016.1203415
Surman M, Janik ME. Stress and its molecular consequences in cancer progression. *Postepy Hig Med Dosw (Online)*. 2017;71(0):485-499. Published 2017 Jun 12. doi:10.5604/01.3001.0010.3830
Activation of "epithelial-mesenchymal transition" (one way new cancer stem cells are formed)
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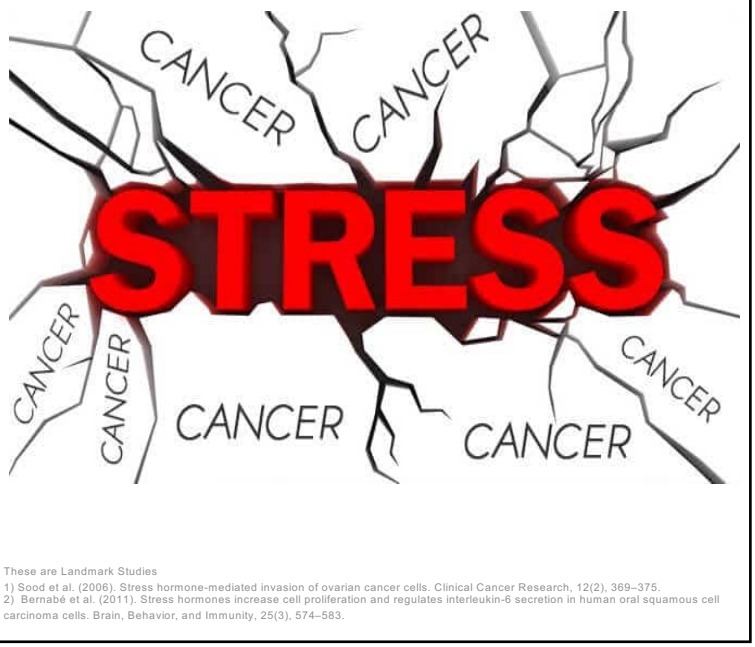
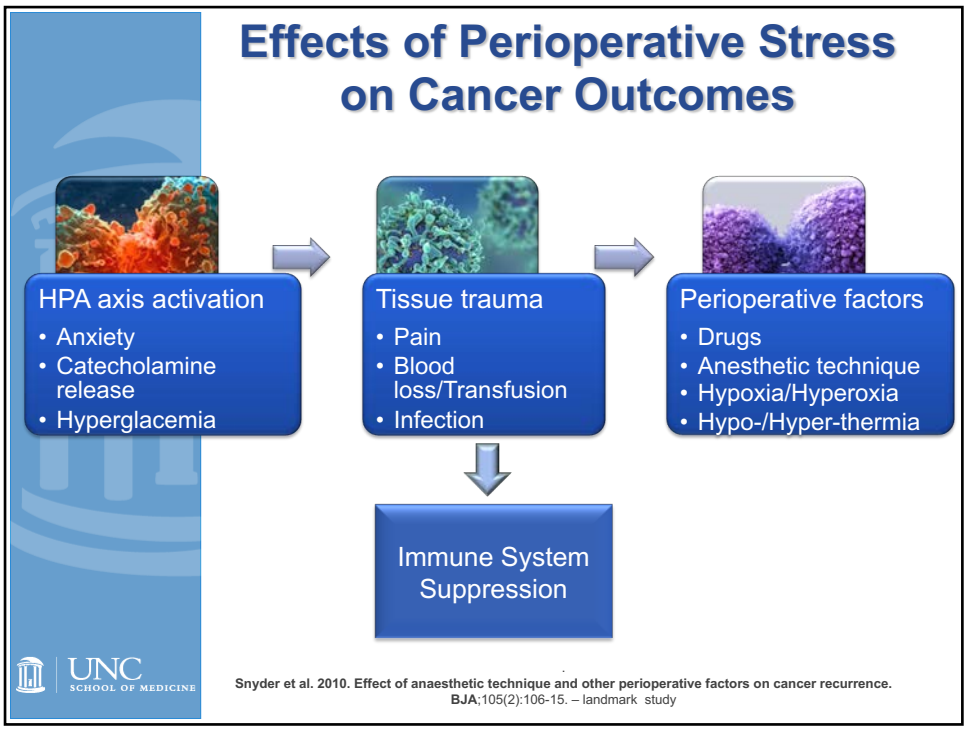
Image adopted from

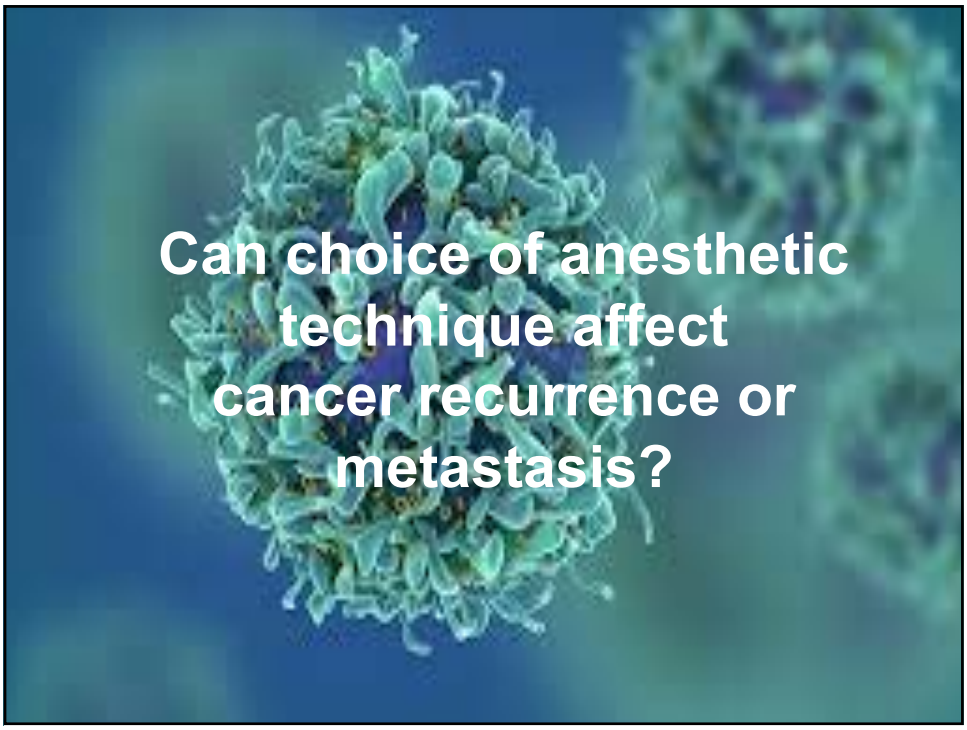
11


CANCER
CANCER
STRESS
CANCER
CANCER
CANCER
CANCER
UNC SCHOOL OF MEDICINE
These are Landmark Studies
1) Sood et al. (2006). Stress hormone-mediated invasion of ovarian cancer cells. Clinical Cancer Research, 12(2), 369–375.
2) Bernabé et al. (2011). Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain, Behavior, and Immunity, 25(3), 574–583.

12


Effects of Perioperative Stress on Cancer Outcomes
HPA axis activation
• Anxiety
• Catecholamine release
• Hyperglacemia
Tissue trauma
• Pain
• Blood loss/Transfusion
• Infection
Perioperative factors
• Drugs
• Anesthetic technique
• Hypoxia/Hyperoxia
• Hypo-/Hyper-thermia
Immune System Suppression
UNC SCHOOL OF MEDICINE
Snyder et al. 2010. Effect of anaesthetic technique and other perioperative factors on cancer recurrence.
BJA;105(2):106-15. – landmark study

13


Can choice of anesthetic technique affect cancer recurrence or metastasis?

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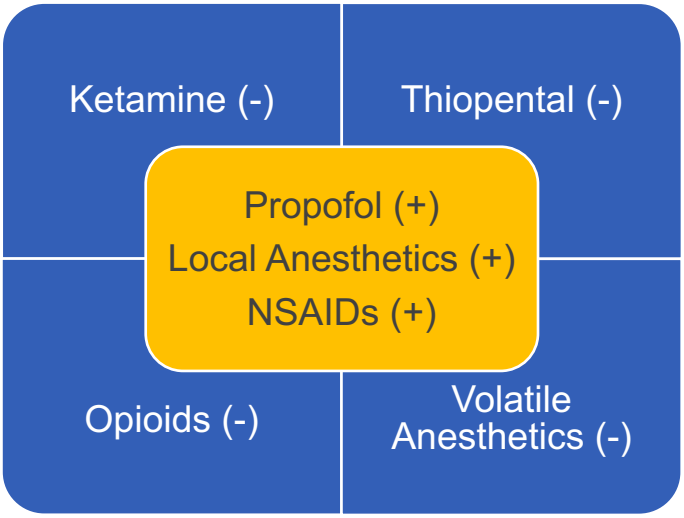
Perioperative Anesthetic Drugs and Cancer Outcomes



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Melamed, et al. (2003). Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. Anesthesiaa & Analgesia, 97(5), 1331–1339

15

Effects of Opioids on Cancer Outcomes

- Meserve et al. (2014). The role of analgesics in cancer propagation. Best Practice & Research Clinical Anaesthesiology, 28(2), 139–151.
- Ma et al. Morphine enhances renal cell carcinoma aggressiveness through promotes surviving level. Ren Fail. 2017 Nov;39(1):258-264
- Cao et al. Morphine, a potential antagonist of cisplatin cytotoxicity, inhibits cisplatin-induced apoptosis and suppression of tumor growth in nasopharyngeal carcinoma xenografts. Sci Rep. 2016 Jan 5;6:18706.
- Nguyen et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. British Journal of Anaesthesia. 2014;113(Suppl 1):i4–13.

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16

Effects of Volatile Anesthetics on Cancer Outcomes

- Tazawa at al. The effect of different anesthetics on tumor cytotoxicity by natural killer cells. Toxicol Lett. 2017 Jan 15;266:23-31.
- Zhang et al. Isoflurane promotes non-small cell lung cancer malignancy by activating the Akt-Mammalian Target of Rapamycin (m-TOR) signaling pathway. Med Sci Monit. 2016 Nov 29;22:4644-4650.
- Iwasaki et al. Volatile anaesthetics enhance the metastasis related cellular signalling including CXCR2 of ovarian cancer cells. Oncotarget. 2016 May 3;7(18):26042-56
- Benzonana et al. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential via the hypoxia inducible factor cellular signaling pathway in vitro. Anesthesiology. 2013 Sep;119(3):593-605.

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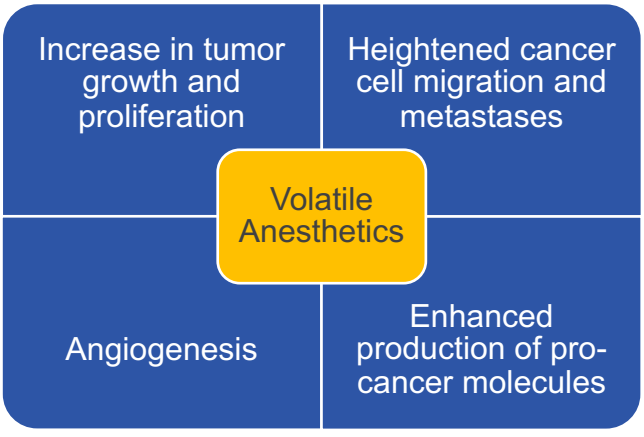
Effects of Volatile Anesthetics on Cancer Outcomes



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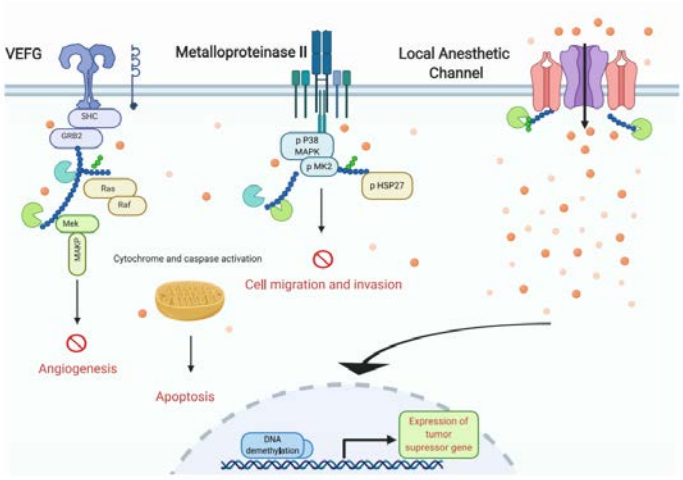
Local Anesthetics:

- potentiate cytotoxicity of the natural killer cells
- facilitate antigen presentation
- modulate function of neutrophils, macrophages, and dendritic cells

Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia Options and the Recurrence of Cancer: What We Know so Far?. *Local Reg Anesth*. 2020;13:57-72. Published 2020 Jul 7. doi:10.2147/LRA.S240567

19

How Do Local Anesthetics Influence Cancer Outcomes?



UNC SCHOOL OF MEDICINE

Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia Options and the Recurrence of Cancer: What We Know so Far?. *Local Reg Anesth*. 2020;13:57-72. Published 2020 Jul 7. doi:10.2147/LRA.S240567

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So where do we go from here?

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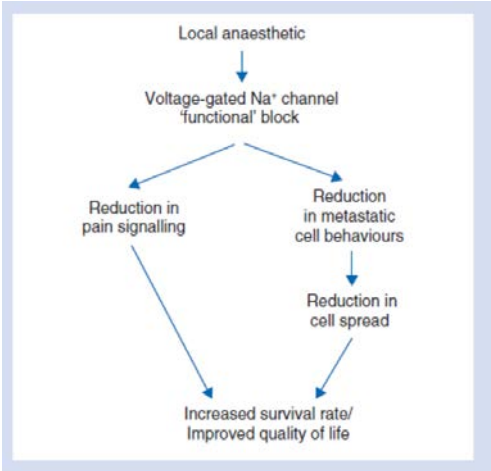
British Journal of Anaesthesia 113 (6): 899–902 (2014)
Advance Access publication 16 July 2014 · doi:10.1093/bja/aeu221

Local anaesthetic use in cancer surgery and disease recurrence: role of voltage-gated sodium channels?

S. P. Fraser[1*], I. Foo[2] and M. B. A. Djamgoz[1]



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NSAIDS Improve Cancer Outcomes

- Chronic aspirin use decreases risk of colon cancer
- COX 2 enzyme tumor overexpression
- COX-2 inhibitors induce tumor cell apoptosis
- COX-2 inhibitors improve response to chemo-therapy in lung cancer
- Ketorolac and diclofenac improve disease free survival in breast cancer
- NSAIDs appear to improve disease free survival and overall survival after cancer surgery

Hou et al. BJ of Clinical Pharm, 2015

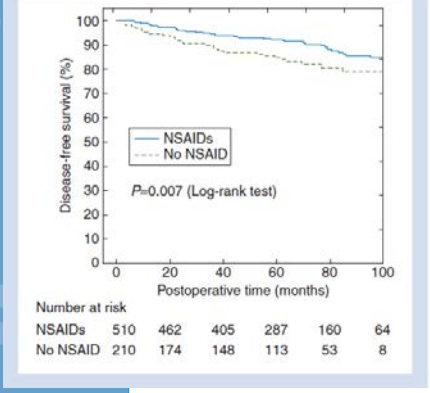
Forget et al. BJA 2014

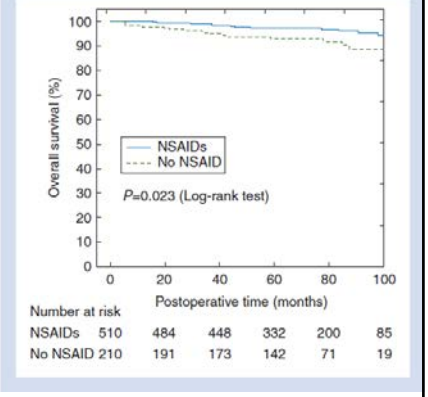
23

British Journal of Anaesthesia 113 (S1): i82–i87 (2014)
Advance Access publication 23 January 2014 · doi:10.1093/bja/aet464

Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery

P. Forget[1*], C. Bentin[2], J.-P. Machiels[3], M. Berliere[2], P. G. Coulie[4] and M. De Kock[1]





Forget BJA 2014

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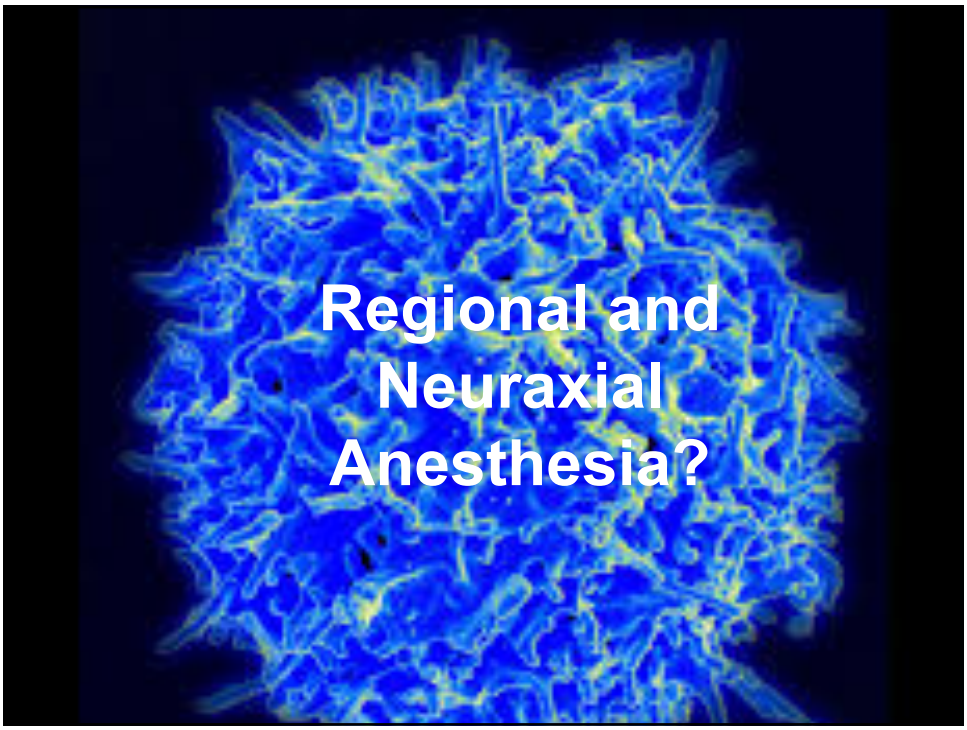

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Benefits of epidural analgesia

- Improved peri-opertive pain control
- Better functional recovery
- Decreased stress response
- Inhibition of catecholamine release results in decreased cardiac O2 demand
- Decreased risk of vascular thrombosis/PE
- Reduced incidence of post-op infections and improved wound healing
- Decreased catabolic state resulting in improved glucose control and decreased protein catabolism

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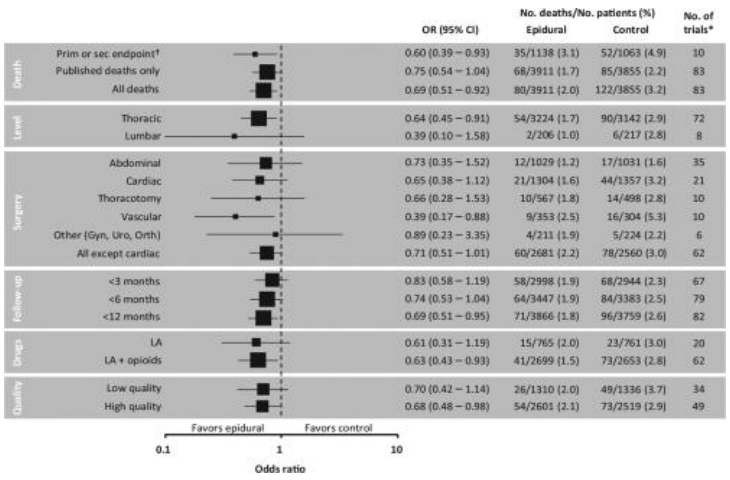
Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anesthesia: results from overview of randomized trials. BMJ. 2000;321:1493 – Landmark Study

26

Epidural Analgesia Decreases Perioperative Morbidity and Mortality



Poppin et al. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials 2014

27

Regional Analgesia

- Avoidance of volatile agents
- Diminished perioperative stress response
- Improved cancer outcomes
- Improved immune system function
- Limited opioid use

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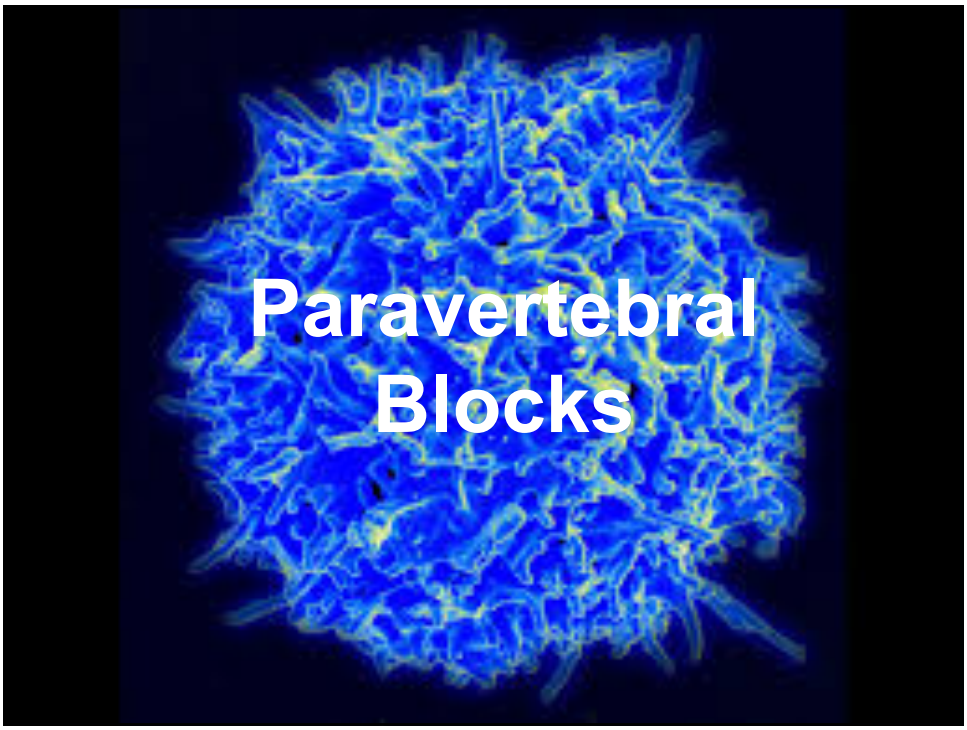
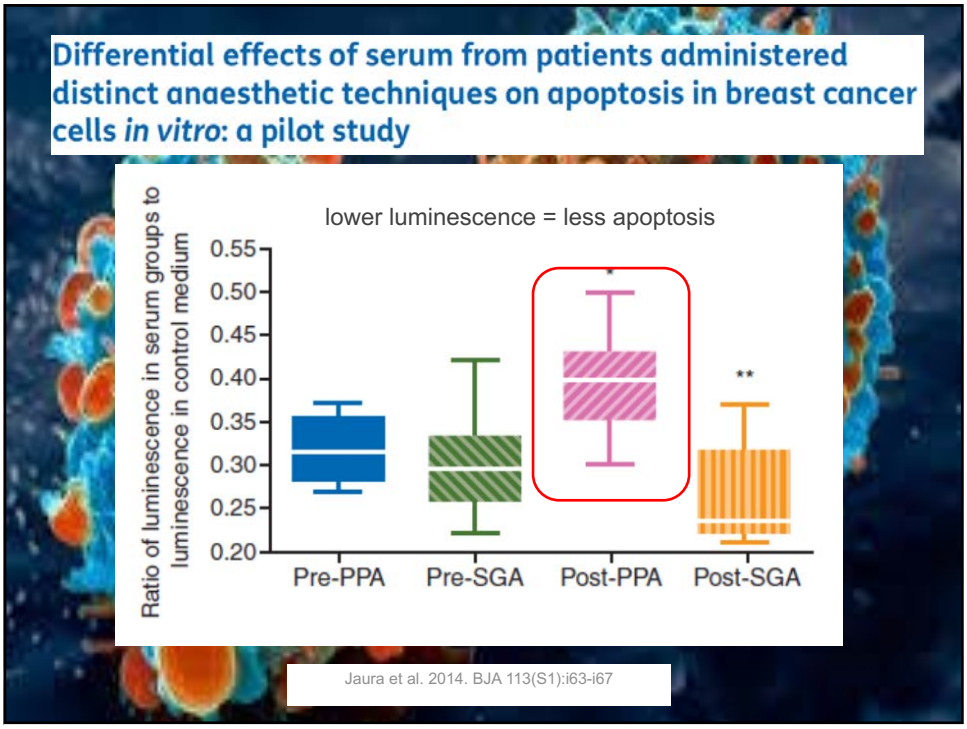
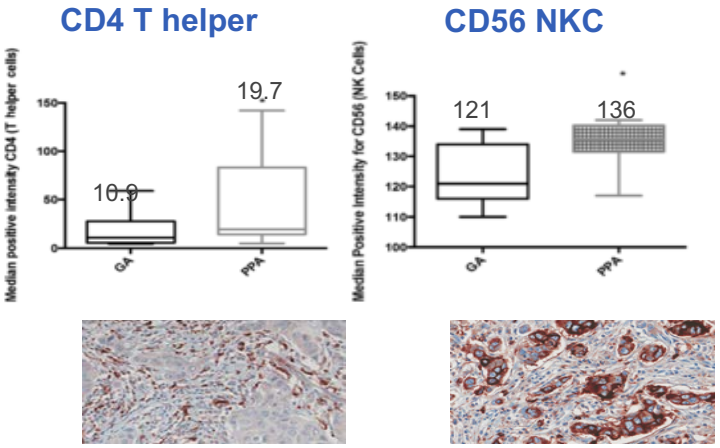

Paravertebral
Blocks

29


Differential effects of serum from patients administered distinct anaesthetic techniques on apoptosis in breast cancer cells *in vitro*: a pilot study
lower luminescence = less apoptosis
Ratio of luminescence in serum groups to luminescence in control medium
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
*
**
Pre-PPA
Pre-SGA
Post-PPA
Post-SGA
Jaura et al. 2014. BJA 113(S1):i63-i67

30

Effect of Anesthetic Technique on Immune Cell Infiltration in Breast Cancer



Desmond et al. 2015. *Anticancer Research vol. 35 no. 3 1311-1319*

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Breast Cancer Surgery GA vs GA + Paravertebral Block (PVB)

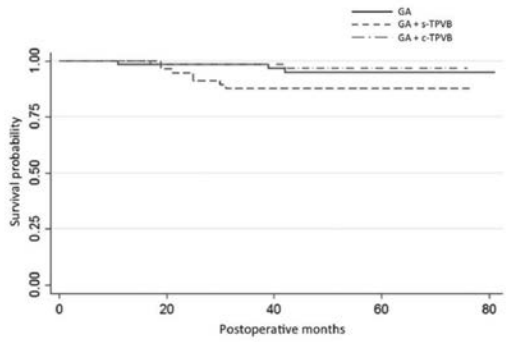

Figure 3. *Survival probability estimates by group. GA: General anesthesia; GA + s-TPVB: general anesthesia plus single-shot thoracic paravertebral block with placebo infusion; GA + c-TPVB: general anesthesia plus continuous paravertebral block infusion (p=0.15).*

Karmakar MK, Samy W, Lee A, et al. Survival Analysis of Patients with Breast Cancer Undergoing a Modified Radical Mastectomy With or Without a Thoracic Paravertebral Block: a 5-Year Follow-up of a Randomized Controlled Trial. *Anticancer Res.* 2017;37(10):5813-5820.

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Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: *A Systematic Review of the Literature*

Oscar Pérez-González, MD[*,†,‡], Luis F. Cuéllar-Guzmán, MD[*,‡], José Soliz, MD[§] and Juan P. Cata, MD[‡,§]

- 467 relevant studies
- 15 were reviewed
- No data to support or refute the use of PVB for reduction of cancer recurrence or survival

Reg Anesth Pain Med. 2017;42(6):751-756.

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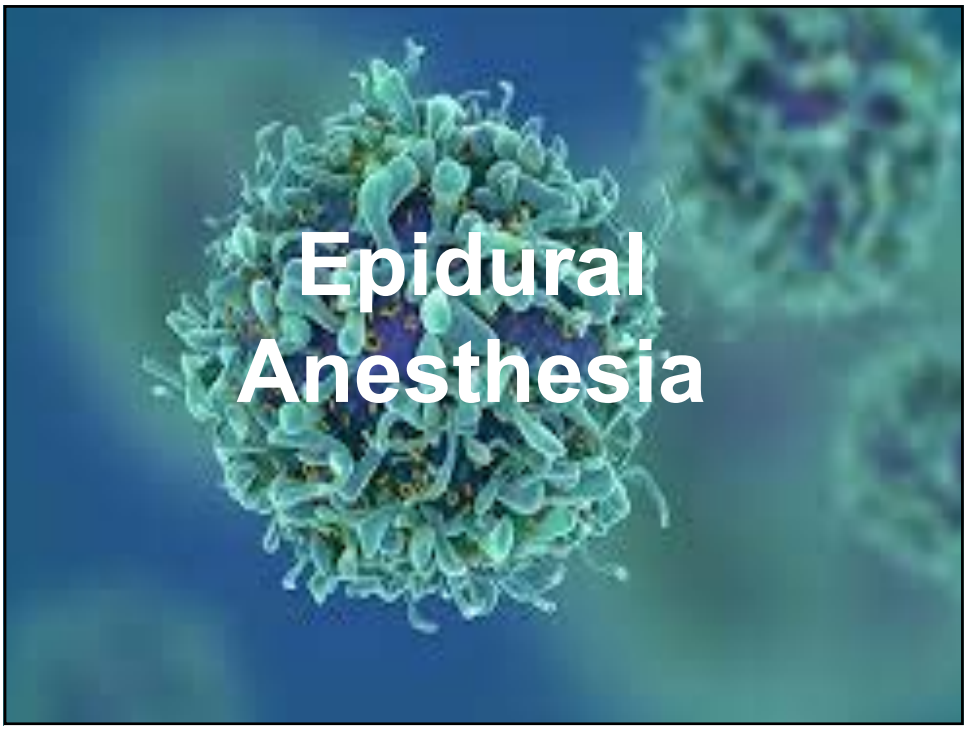

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Epidural Analgesia in Cervical Carcinoma

- N=85
- GETA/EPI vs GETA
- Natural Killer cells activity measured before anesthesia, at incision, 4 and 24 hrs hours after
- GETA/EPI group:
  - » Decreased suppression of NK activity
  - » Increased levels of antitumorigenic (IL-2 and IFN-γ)
  - » and decreased levels of protumorigenic (IL-1β, IL-6,1L-8) cytokines

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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(6):703-707.

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Epidural analgesia associated with better survival in colon cancer

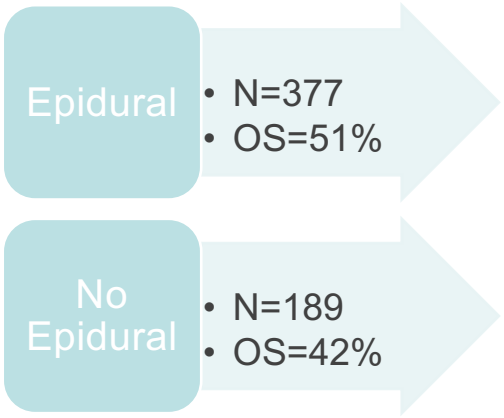

FIG1
OS = overall survival rates in %

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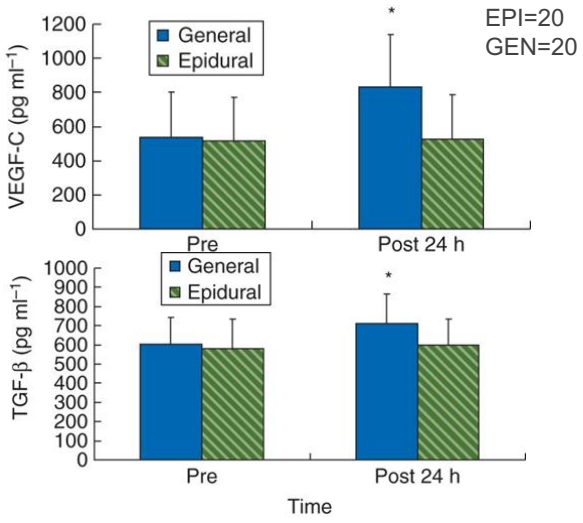
Vogelaar et al. Int J Colorectal Dis. 2015 Aug;30(8):1103-7.

36

Effect of thoracic epidurals on tumor promoting serum factor levels in colon cancer surgery



Xu et al. British Journal of Anesthesia 113 (S1): i49–i55 (2014)

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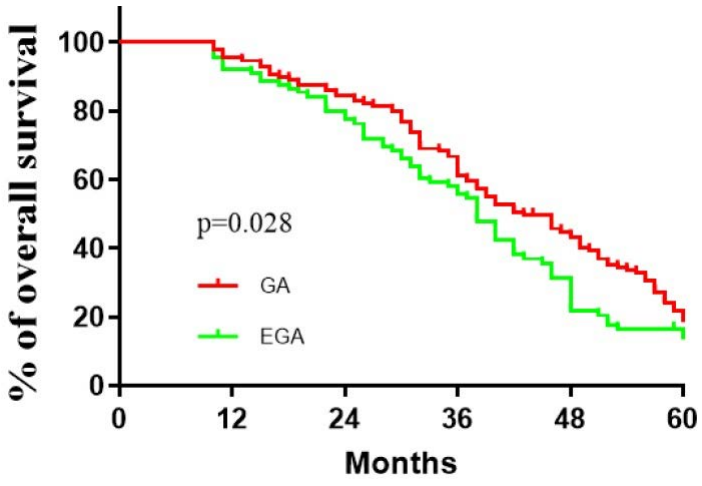
Colorectal Surgery



Gao H, Meng X-Y, Wang H-Q, et al. Association between anaesthetic technique and oncological outcomes after colorectal carcinoma liver metastasis resection. Int J Med Sci. 2019;16(2):337–342. doi:10.7150/ijms.28016

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Colorectal Surgery

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Colorectal	Cummings (2012)[61]	Retrospective	EA-GA vs GA	No difference	Increased with GA-EA
Colorectal	Gottschalk (2010)[62]	Retrospective	EA-GA vs GA	Not studied	No difference
Colorectal	Gupta (2011)[63]	Retrospective	EA-GA vs Spinal vs GA	Increased for rectal cancer, no difference for colon cancer	Not studied
Colorectal	Day (2012)[64]	Retrospective	EA-GA vs Spinal vs GA	No difference	No difference
Colorectal	Kim (2016)[65]	RCT	LA wound infiltration vs IVPCA	Not studied	No difference
Colorectal liver metastasis	Zimmitti (2016)[66]	Retrospective	EA-GA vs GA	No difference	Increased with EA-GA
Colorectal liver metastasis	Gao (2019)[67]	Retrospective	EA-GA vs GA	Not studied	Increased with GA

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Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia Options and the Recurrence of Cancer: What We Know so Far?. *Local Reg Anesth*. 2020;13:57-72. Published 2020 Jul 7. doi:10.2147/LRA.S240567

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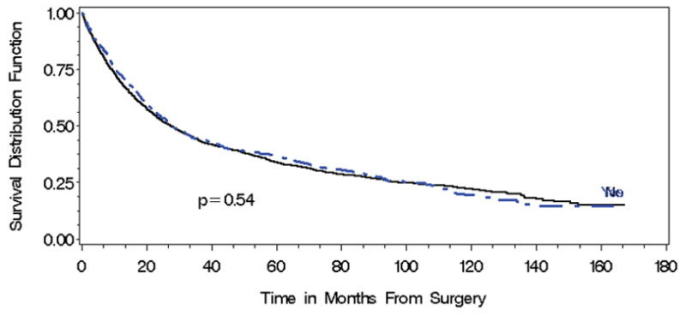
Epidural vs Opioid Pain Management in Gastric Cancer Surgery

- Retrospective chart review study
- N 2745 (766 EPI)
- Outcome: Overall survival



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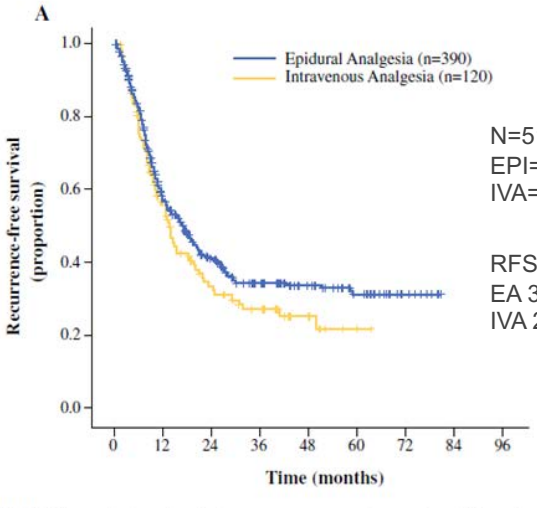
Cummings et al. Reg Anesth Pain Med. 2014:May-Jun;39(3):200-7.

40

Colorectal Cancer with Liver Metastases



N=510
EPI=390
IVA= 120

RFS
EA 34.7%
IVA 21.1%

Zimitti et al, Annals of Surgical Oncology, 2016

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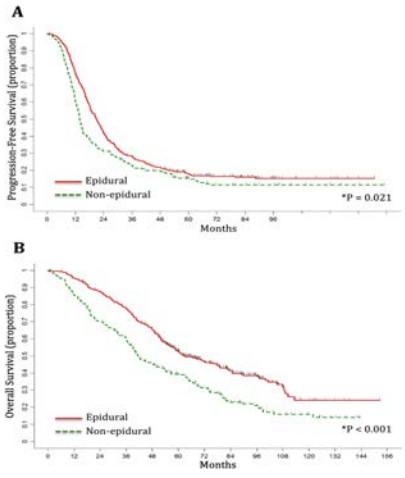
Ovarian Cancer



Tseng JH, Cowan RA, Afonso AM, et al. Perioperative epidural use and survival outcomes in patients undergoing primary debulking surgery for advanced ovarian cancer. *Gynecol Oncol.* 2018;151(2):287-293. doi:10.1016/j.ygyno.2018.08.024

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Ovarian Cancer

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Ovarian	De Oliveira (2011)[79]	Retrospective	EA (intra and postop)-GA vs Postop-only EA vs IVPCA	Not studied	Increased with EA-GA
Ovarian	Lin (2011)[80]	Retrospective	EA vs GA-IVPCA	Increased with EA	Not studied
Ovarian	Capmas (2012)[81]	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Lacassie (2013)[82]	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Tseng (2018)[83]	Retrospective	EA vs IV-PCA	Increased with EA	Increased with EA
Ovarian	Zhong (2019)[84]	Retrospective	EA vs GA-IVPCA	No difference	Not studied
Ovarian	Elias (2015)[85]	Retrospective	EA-GA vs GA	Not studied	No difference

Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia Options and the Recurrence of Cancer: What We Know so Far?. *Local Reg Anesth*. 2020;13:57-72. Published 2020 Jul 7. doi:10.2147/LRA.S240567

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Prostate cancer

- **Lee et al.** Pain Management. 2015
- Meta-analysis
- 10 retrospective studies
- GA 6261/EPI7504
- Regional anesthesia improved OS
- No decrease in RFS
- RRM (relative risk of mortality) reduced by 19%

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Lee et al. Pain Management. 2015;,5(5):387-395

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Pancreatic Cancer

- Study designed to evaluate the effects of dexamethasone on pancreatic cancer survival
- Use of perioperative epidural associated with increased survival
- No difference in GA or opioid administration between EPI and NO EPI groups
- Benefits of both dexamethasone and epidurally administered local anesthetics (LAs) were attributed to their anti-inflammatory effects, and in case of amide LAs to their anti-proliferative effects on mesenchymal cells.

Tyler et al. Factors Associated with Improved Survival after Resection of Pancreatic Adenocarcinoma: A Multivariable Model. Anesthesiology 2 2015, Vol.122, 317-324.

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Weaknesses of Current Evidence

- Type of surgical procedure/approach
- Use of adjuvant cancer therapy
  - XRT
  - Chemo
  - Hormone therapy
  - Immunotherapy
- Type of anesthetic technique
  - GETA (volatile anesthetic) vs TIVA (propofol, LA)
  - Opioids
  - Ketamine
- Intraoperative variables
  - Hypo-/Hyper-thermia
  - Hypo-/Hyper-oxia
  - Anemia/Tansfusion

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Ongoing Research

Breast cancer
- N 1100, prospective/randomized
- Completion 2019

Colon cancer
- N 2500, prospective/randomized
- Completion 2022

Lung cancer
- N 1532, prospective/randomized
- Completion 2018

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Thank you!

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