

## Benefits of Regional Anesthesia in Cancer Surgery

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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



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### Cancer Therapy

Treatment category	Specific treatments
<b>Surgery</b> <small>Surgeon</small>	<ul style="list-style-type: none"> <li>• Lumpectomy</li> <li>• Lymph node dissection (seminal and axillary)</li> <li>• Mastectomy</li> </ul>
<b>Radiation therapy</b> <small>Radiation Oncologist</small>	<ul style="list-style-type: none"> <li>• External beam (3D conformal, IMRT)</li> <li>• Brachytherapy (High dose [HDR] or low dose [LDR])</li> <li>• Intraoperative radiation (IORT)</li> </ul>
<b>Systematic therapy</b> <small>Medical Oncologist</small> <small>(attack cancer cells throughout the body)</small>	<ul style="list-style-type: none"> <li>• Chemotherapy</li> <li>• Hormone therapy</li> <li>• Targeted drug therapy</li> </ul>



Cancer Remission
Cancer Recurrence  
Death

Adopted from jeffysterlingmd.com

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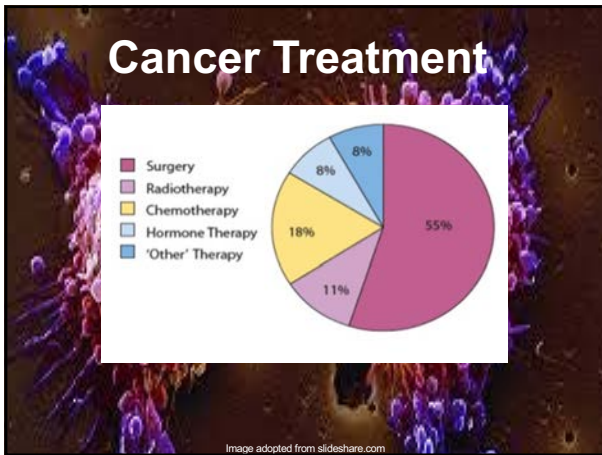
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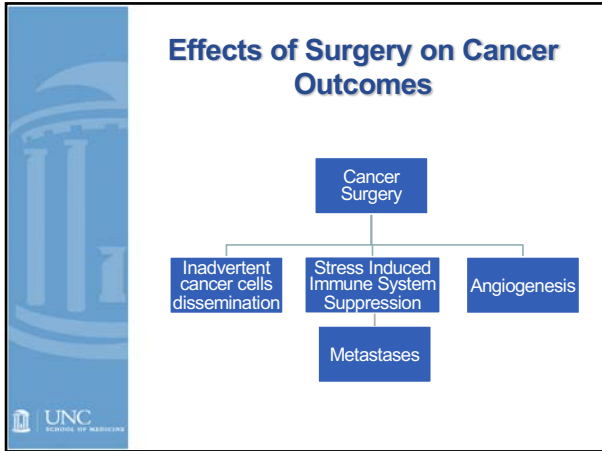
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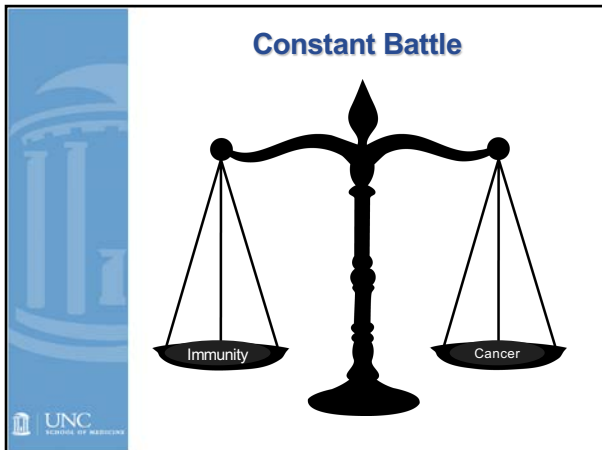
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### Why is cancer so tough to kill?



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

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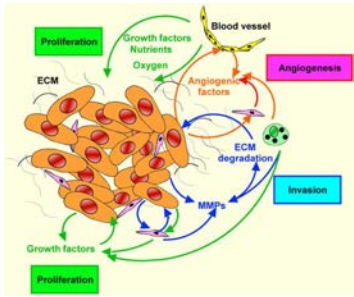
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### Tumor Microenvironment



1) Koorngbae 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.cancer.com/V04-0068.htm>

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### Function of the Immune System in Cancer Detection

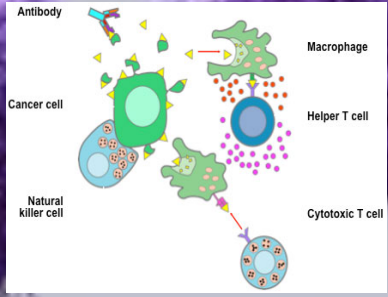


Image adopted from National Cancer Institute

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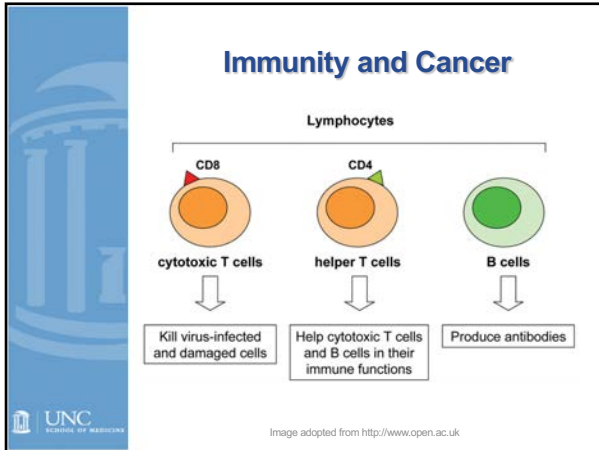
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**7 Cancer-Promoting Processes**

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:10.5604/01.3001.0010.10.3830

✓ Activation of "epithelial-mesenchymal transition" (one way new cancer stem cells are formed)

Image adopted from

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**STRESS**

CANCER

CANCER

CANCER

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CANCER

CANCER

These are Lancet Studies  
 1) Sood et al. (2008). 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.

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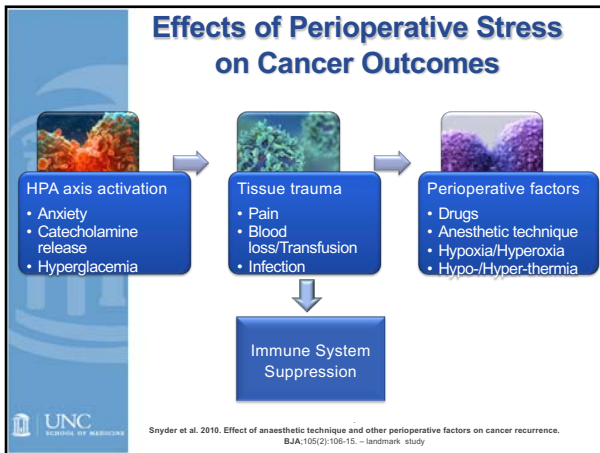
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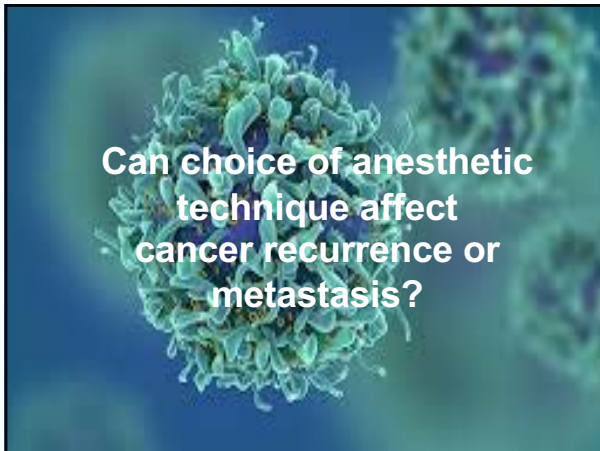
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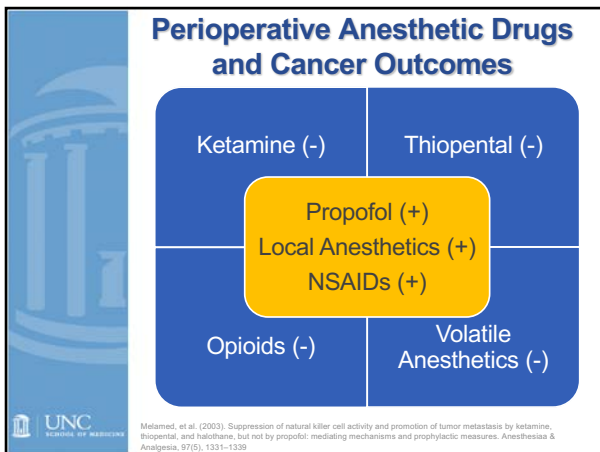
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**Effects of Opioids on Cancer Outcomes**

- 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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**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**

Increase in tumor growth and proliferation	Heightened cancer cell migration and metastases
Volatile Anesthetics	
Angiogenesis	Enhanced production of pro-cancer molecules




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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

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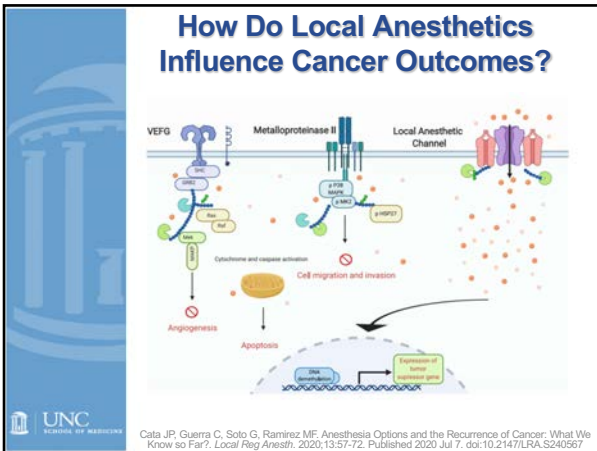
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Cata JP, Guerra C, Soto G, Ramirez MF. Anesthesia Options and the Recurrence of Cancer: What We Know so Far?. *Local Reg Anesth.* 2020;13:57-72. Published 2020 Jul 7. doi:10.2147/LRA.S240567

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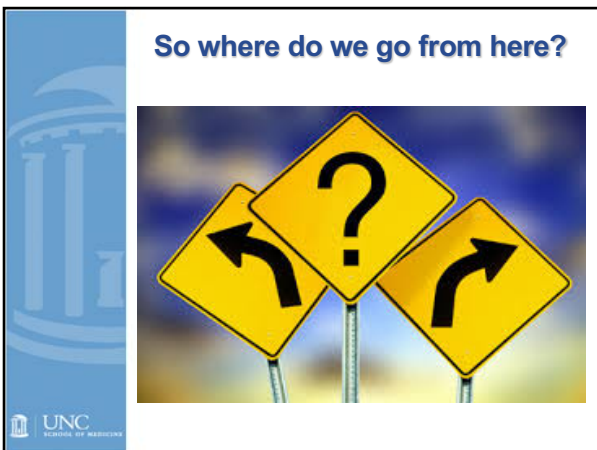
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British Journal of Anaesthesia 113 (6): 899-902 (2014)  
Advance Access publication 16 July 2014 · doi:10.1093/bjaeu221

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

S. P. Fraser<sup>1</sup>\*, I. Foo<sup>2</sup> and M. B. A. Djamgoz<sup>1</sup>

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    graph TD
      A[Local anaesthetic] --> B[Voltage-gated Na+ channel "functional" block]
      B --> C[Reduction in pain signalling]
      B --> D[Reduction in metastatic cell behaviours]
      D --> E[Reduction in cell spread]
      C --> F[Increased survival rate/Improved quality of life]
      E --> F
  
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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 chemotherapy 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

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British Journal of Anaesthesia 113 (5): 480-487 (2014)  
Advance Access publication: 12 January 2014 · doi:10.1093/bja/aeu154

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

P. Forget<sup>1</sup>\*, C. Bentin<sup>1</sup>, J.-P. Mochiels<sup>1</sup>, M. Bertiere<sup>2</sup>, P. G. Coulie<sup>4</sup> and M. De Kock<sup>1</sup>

Postoperative time (months)	0	20	40	60	80	100
NSAIDs	510	462	405	287	160	64
No NSAID	210	174	148	113	53	8

Postoperative time (months)	0	20	40	60	80	100
NSAIDs	510	484	448	332	200	85
No NSAID	210	191	173	142	71	19

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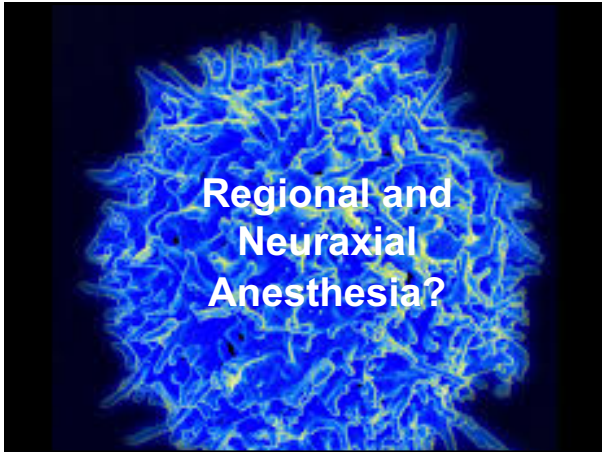
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### Benefits of epidural analgesia

- Improved peri-operative pain control
- Better functional recovery
- Decreased stress response
- Inhibition of catecholamine release results in decreased cardiac O<sub>2</sub> 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

Roggers 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

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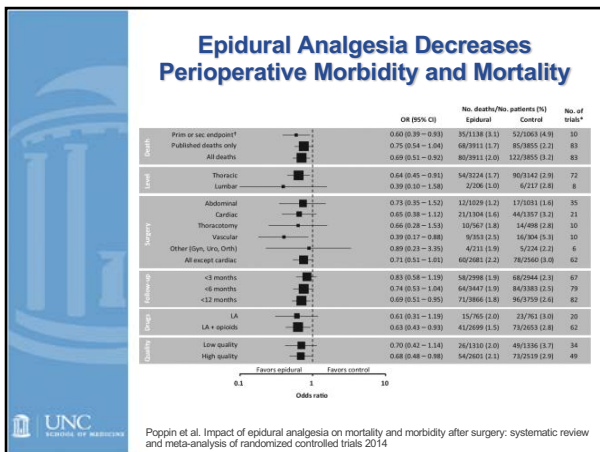
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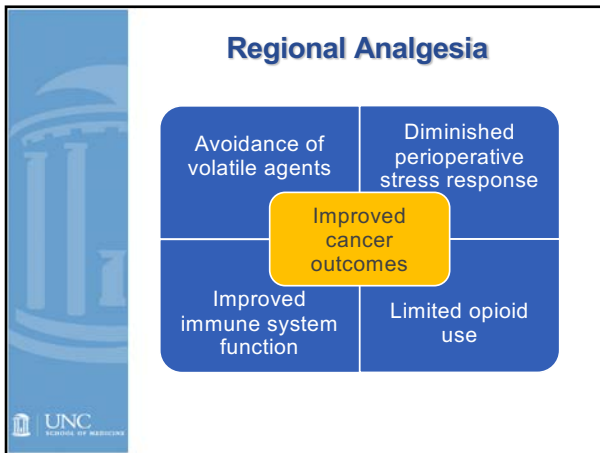
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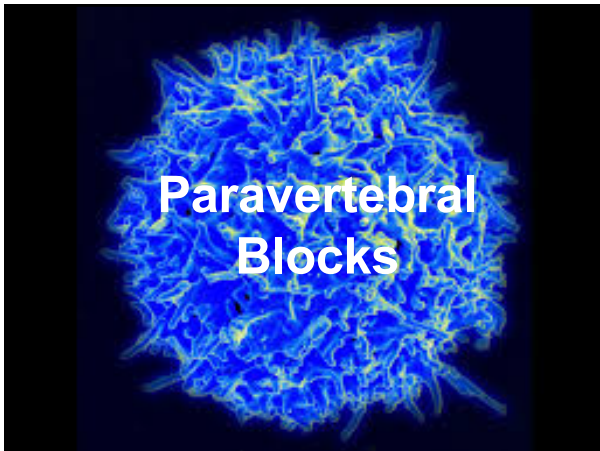
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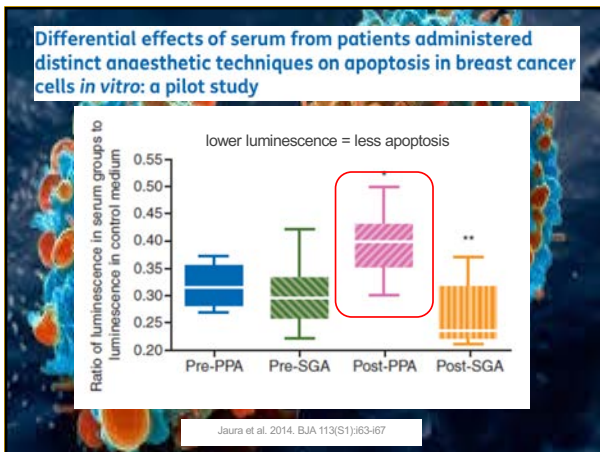
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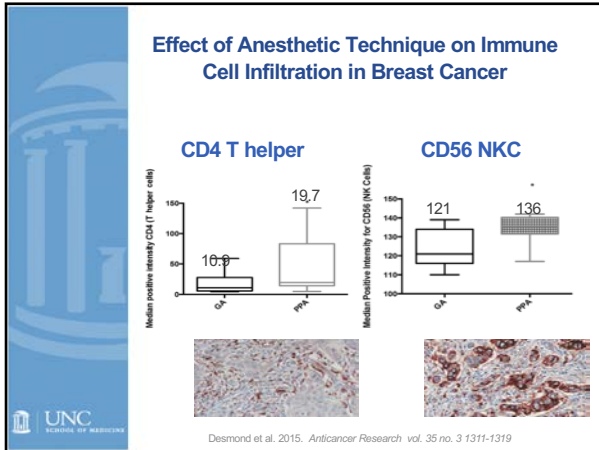
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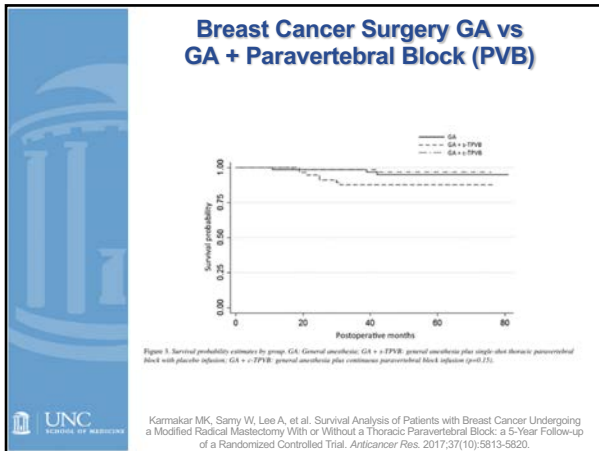
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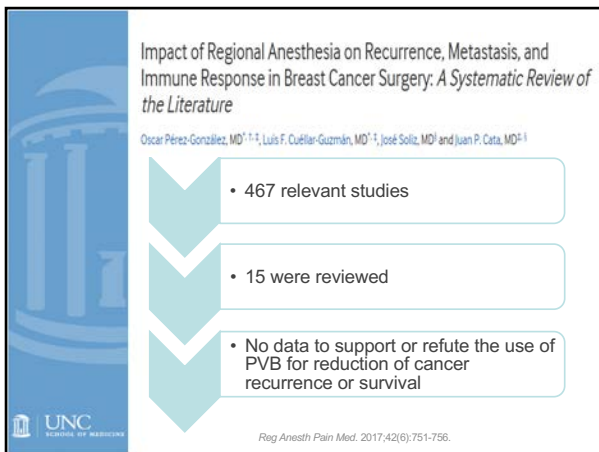
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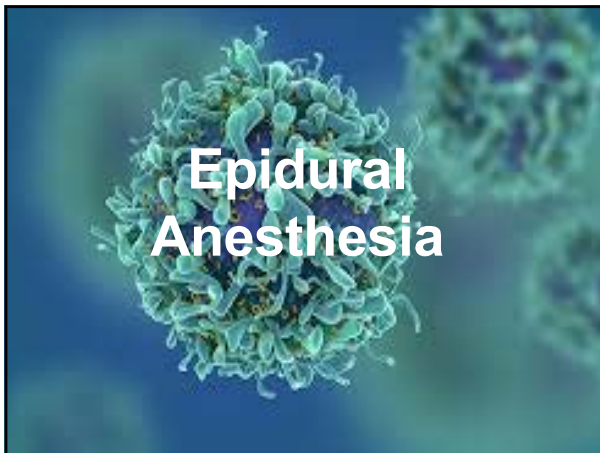
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**Epidural Analgesia in Cervical Carcinoma**

- 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- $\gamma$ )
  - » and decreased levels of protumorigenic (IL-1 $\beta$ , IL-6,1L-8) cytokines

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;38(6):703-707.

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**Epidural analgesia associated with better survival in colon cancer**

Epidural	• N=377 • OS=51%
No Epidural	• N=189 • OS=42%

FIG1  
OS = overall survival rates in %

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

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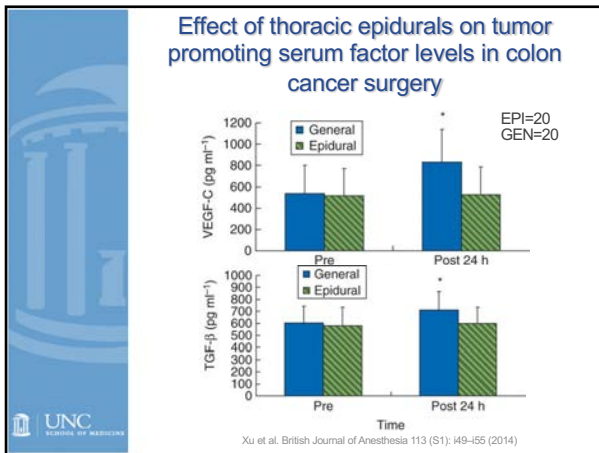
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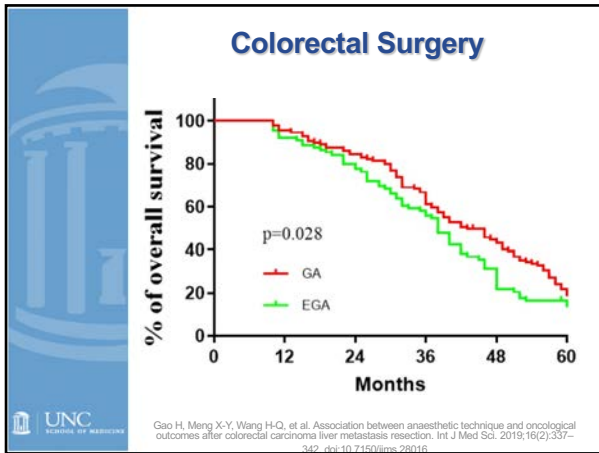
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### Colorectal Surgery

Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Colorectal	Cummings (2012) <sup>11</sup>	Retrospective	EA-GA vs GA	No difference	Increased with GA-EA
Colorectal	Gomtschik (2010) <sup>12</sup>	Retrospective	EA-GA vs GA	Not studied	No difference
Colorectal	Gupta (2011) <sup>13</sup>	Retrospective	EA-GA vs Spinal vs GA	Increased for rectal cancer; no difference for colon cancer	Not studied
Colorectal	Dey (2013) <sup>14</sup>	Retrospective	EA-GA vs Spinal vs GA	No difference	No difference
Colorectal	Kim (2014) <sup>15</sup>	RCT	LA wound infiltration vs IVPCA	Not studied	No difference
Colorectal liver metastasis	Zinnati (2014) <sup>16</sup>	Retrospective	EA-GA vs GA	No difference	Increased with EA-GA
Colorectal liver metastasis	Gas (2019) <sup>17</sup>	Retrospective	EA-GA vs GA	Not studied	Increased with GA

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

Survival Distribution Function

Time in Months From Surgery

p=0.54

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

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### Colorectal Cancer with Liver Metastases

Recurrence-free survival (proportion)

Time (months)

— Epidural Analgesia (n=390)  
— Intravenous Analgesia (n=120)

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

Progression-free survival (months)

Overall survival (months)

— Epidural  
— Non-epidural

p=0.021

p=0.001

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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Type of Cancer	Author (Year)	Type of Study	Intervention	Overall Survival	Recurrence-Free Survival
Ovarian	De Oliveira (2011) <sup>28</sup>	Retrospective	EA (intra and postop)-GA vs Postop-only EA vs IVPCA	Not studied	Increased with EA-GA
Ovarian	Lin (2011) <sup>29</sup>	Retrospective	EA vs GA-IVPCA	Increased with EA	Not studied
Ovarian	Capmas (2012) <sup>30</sup>	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Lacasse (2013) <sup>31</sup>	Retrospective	EA vs No EA	No difference	No difference
Ovarian	Tsang (2018) <sup>32</sup>	Retrospective	EA vs IV-PCA	Increased with EA	Increased with EA
Ovarian	Zhong (2019) <sup>33</sup>	Retrospective	EA vs GA-IVPCA	No difference	Not studied
Ovarian	Elas (2015) <sup>34</sup>	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%

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* 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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