Anesthesia for Oncology Surgery: Does Anesthesia Choice Impact Outcomes?

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Objectives

- Review the carcinogenesis model and “two-hit” hypothesis
- Review the principles for anesthesia care of the oncology patient
- Describe the literature findings related to anesthetic agent choice and cancer recurrence
3000 BC- the word cancer was not used, the oldest description of the disease is from Egypt. It is called the Edwin Smith Papyrus. It describes 8 cases of tumors or ulcers of the breast that were treated by cauterization with a tool called the fire drill. The description adds that there is not treatment for the condition.

460-370 BC. The disease was first called cancer by Greek physician Hippocrates. He is considered the “Father of Medicine.” Hippocrates used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors. In Greek this means a crab.

## Cancer Statistics

### Estimated new cases, 2018

By cancer type, both sexes combined

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>268,670</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>234,030</td>
</tr>
<tr>
<td>Prostate</td>
<td>164,690</td>
</tr>
<tr>
<td>Colorectum</td>
<td>140,250</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>91,270</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>81,190</td>
</tr>
</tbody>
</table>

### Estimated deaths, 2018

By cancer type, both sexes combined

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>154,050</td>
</tr>
<tr>
<td>Colorectum</td>
<td>50,630</td>
</tr>
<tr>
<td>Pancreas</td>
<td>44,330</td>
</tr>
<tr>
<td>Breast</td>
<td>41,400</td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>30,200</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,430</td>
</tr>
</tbody>
</table>

[https://cancerstatisticscenter.cancer.org/#!/]
The American Cancer Society estimates 1/3 to ½ of Americans will develop cancer in their lifetime BUT not all cancers kill you. Overall, more than 50% of people diagnosed with cancer live for more than 5 years. Some cancers have survival rates of more than 90%.
Research has identified numerous factors that increase an individual’s risk for developing cancer. By modifying behavior, individuals can eliminate or reduce many of these risks and thereby reduce their risk of cancer.

Developing and implementing additional public education and policy initiatives could help further reduce the burden of cancers related to preventable cancer risk factors.

Adapted from (39).
Cancer is in the news!

**Medscape October 2018**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.21</td>
<td>CDK Inhibitor Therapy in HR+/HER2- Advanced Breast Cancer: Clinical Characteristics and Choices</td>
</tr>
<tr>
<td>10.21</td>
<td>Systemic Lupus Erythematosus: Charting a Course for Improved Outcomes</td>
</tr>
<tr>
<td>10.22</td>
<td>HER2-Positive Breast Cancer and Resistance: What Next</td>
</tr>
<tr>
<td>10.22</td>
<td>Treating Cancer-Associated Thrombosis Today: New Concepts and Perspectives</td>
</tr>
<tr>
<td>10.27</td>
<td>Advanced Hodgkin Lymphoma: How Can We Do Better?</td>
</tr>
</tbody>
</table>
Cancer Incidence

- **2012 → 2030**
  - Worldwide cancer cases are projected to increase by **50%**
  - From **14 million** to **21 million**

- **2004 → 2013**
  - The overall cancer death rate in the United States fell by **13%**
  - Worldwide cancer deaths are projected to increase by **60%**
  - From **8 million** to **13 million**

https://www.cancer.gov/about-cancer/understanding/statistics
Carcinogenesis Model

https://www.slideshare.net/docsartorfaqeer/carcinogenic-agents-and-their-cellular-interactions
Early detection
Upstream data fusion (UDF)

• Traditional breast cancer identified by Chest-X ray
• New ex military imaging software allows overlapping of multimodal imaging to obtain early diagnosis
• Ideally ultrasound, Chest X ray and MRI imaging is combined. Initial studies with CXR and MRI improved from 86.8 to 94.1% detection rate and separation of malignancy from benign tumors

Breast Cancer Multi-Modality/Exam Detection (MMED) Using Upstream Data Fusion (UDF)
Knudson Two-Hit Hypothesis

In order for a particular cell to become cancerous, both of the cell's tumor suppressor genes must be mutated. This idea is known as the "two-hit" hypothesis, and it was first proposed by geneticist Alfred Knudson in 1971.

- Original work in retinoblastoma
- Activation of Proto-oncogene
- Deactivation of tumor suppressor genes

NHS National Genetics Education and Development Centre Genetics and Genomics for Healthcare [www.geneticseducation.nhs.uk](http://www.geneticseducation.nhs.uk)
2013—Actress Angelina Jolie announced in a New York Times op-ed article on Tuesday that she underwent a preventive double mastectomy after learning that she carries a mutation of the **BRCA1 gene**, which sharply increases her risk of developing breast cancer and ovarian cancer.

It has been estimated that the lifetime risk of breast cancer in women with a BRCA1 or BRCA2 mutation ranges from about 50% to 85% compared to 12% in the general population.

- [https://www.cnn.com/2013/05/14/showbiz/angelina-jolie-double-mastectomy/index.html](https://www.cnn.com/2013/05/14/showbiz/angelina-jolie-double-mastectomy/index.html)
Suppressing Cancer Cells

Caretaker Genes

Immune System

• Natural Killer Cells- bodies primary defense

• Cystotoxic T-Cells

• T-Helper cells $T_H^1$ ( produce interferon)

• Dendritic cells

First RNA-based therapy approved in US and Europe

Gene-silencing technique works without altering the person’s DNA, and prevents harmful proteins from being made in their cells

In August, a new therapy – the first of its kind – was approved in the US and Europe to treat a genetic disease- hereditary TTR mediated Amyloidosis. The therapy uses small pieces of RNA to effectively 'silence' a faulty gene, without changing the DNA of the patient.

ANESTHESIA CONSIDERATIONS
Preop Considerations

Correction of derangements
• Nutrient deficiencies
• Electrolyte imbalance
• Hydration status

Adverse effects of treatment
• End organ damage to heart, lung, kidney, liver, hematologic, endocrine and airway
• Risk of thromboembolic events
• Malnutrition-dehydration, impaired wound healing

Chemotherapy Target

- **Goal:** *Selective toxicity*: target rapidly-dividing cells

- **Caveat:** includes some normal cells
  - Bone marrow
  - Gastrointestinal
  - Skin
  - Hair follicles

- Side effects are relative
- Risk of secondary cancer
General Considerations for Anesthesia

• Myelosuppression
• Immunosuppression

• Nadir
  – Erythrocytes: 120 days
  – Thrombocytes: 6-7 days
  – Leukocytes: 4-6 hours
  – Take home-best to wait > 120 days

• Attention to aseptic technique

Chemotherapeutics

- Alkylating agents
- Antibiotic agents
- Antimetabolite agents
- Plant alkaloids
- Nitrosureas
- Enzymes
- Taxanes
- Random Synthetics
- Miscellaneous
Alkylating Agents

- Interfere with mitosis
- Indications
  - Breast and ovarian carcinomas
  - Lymphoma, melanoma, multiple myeloma
- Side effects
  - Myelosuppression (dose limiting factor)
  - Pulmonary fibrosis
  - Plasma pseudocholinesterase inhibition

- Busulfan
- Chlorambucil
- Cyclophosphamide
- Ethylenimine
- Ifosamide
- Mechlor-ethamine
- Melphalan
- Triazine
- Carmustine
- Lomustine
Antimetabolites

• Inhibit normal enzymatic function
  – Analogs of functional cells but are dysfunctional

• Indications
  – GI and pulmonary carcinomas
  – Osteogenic sarcoma
  – Lymphoblastic leukemia
  – Burkett’s lymphoma
Antimetabolites

- Side effects
  - Renal failure
  - Capillary leak syndrome
  - Acute and chronic hepatotoxicity
Antibiotic Agents

• Inhibition of DNA and RNA synthesis

• Wide variety of cancers

• Side effects
  – Cardiac toxicity (>550 mg/m²)
    • Permanent cardiomyopathy
  – Pulmonary fibrosis
Plant Alkaloids

• Terminates M-phase of cell division

• Indications
  – Hodgkin’s Lymphoma
  – Non-Hodgkin’s Lymphoma
  – Testicular Cancer
Plant Alkaloids

• Side effects
  – Neurotoxicity
    • Recurrent laryngeal nerve palsy
    • CNS impairment
    • CN palsies
  – Sensory impairment
  – Substantial leukopenia
Is there an APP for that?

For Patients
• ChemoWave
• CancerAid
• MyMedical
• StupidCancer
• CaringBridge
• Cancer.net Mobile
• DrawerMD

For Healthcare workers
• Epocrates.com
• Lexicomp.com
• Chemocare.com
• Bccancer.bc.ca/health-professionals
• Stanfordhealthcare.org

and search chemotherapy

https://chemowave.com/
https://www.maacenter.org/blog/7-apps-for-cancer-patients/
General Considerations

• Side effects from inadvertently targeted tissues
  – Myelosuppression
  – Nausea and vomiting
  – Diarrhea
  – Stomatitis
  – GI ulceration
• Nadir
• Aseptic technique
Future treatments

Cancer cells commandeer a “don’t eat me” signal, called CD47, to escape elimination by our innate immune system’s first responders. Blocking CD47 “don’t eat me” signals while releasing and boosting “eat me” signals is the core focus of our research to enable the patient’s own immune system to attack and destroy their cancer.

https://www.fortyseveninc.com/science#pipeline
Patient Evaluation

• Bone marrow function
  – Blood product preparedness
  – Antibody formation

• Pulmonary
  – Subjective DOE
  – CXR
  – ABG
Patient Evaluation

• Cardiac
  – ECG & Echo
  – Invasive monitoring
  – Urinary output
  – Anesthesia agent choice

• Hepatic/Renal
  – Evaluation of function
  – Prudent choice of pharmacology
Patient Evaluation

• Neurologic
  – ANS; existing paresthesias
  – CNS; mental status
    • Use of regional anesthesia?

• Agent-specific alterations
  – Pseudocholinesterase deficiency
Does Surgery/Anesthesia Impact Cancer Progression?

Implications of surgery

Incision
Pain
Stress
SNS stimulation
Tissue manipulation
Access to blood stream,
Lymph, vessel walls
Hypothermia
ANESTHESIA TECHNIQUE
Univariable association between paravertebral block and cancer recurrence

Occurrence of Recurrence

• Tumor cells survive after surgery
  – Released during excision
  – Natural Killer Cell

• Avoidance of Immune System
  – Micrometastases
    • Requirements:
      – Mitosis signaling
      – Angiogenic signaling
What We Know
What We Don’t Know

• Prospective randomized research has not been done yet
  – Difficult for many reasons

• Most research is retrospective
  – Although very suggestive...
Induction Agents

Propofol
- Not much action on reducing NK cell activity

Ketamine
- Increases retention of lung tumors

Thiopental
- Immunosuppressant actions
- Reduces NK cell activity

Propofol Benefit?

• Mice inoculated with intraperitoneal tumor cells

• Randomized: Intraperitoneal treatment
  – Saline
  – Propofol
  – Intralipid

• Tumor growth measured

Inhaled Agents

• Breast cancer surgery

• Proliferation of cancer cells in serum postoperatively

• Variable:
  – inhaled+opiod
  – Propofol+block

Inhalation agents

Halogenated

• Reduce NK cell number
• Reduce NK cell function
• Suppress lymphocytes
• Attenuate interferon production
• Alter release of tumor necrosis factor (TNF)
• Alter release of cytokines
• Increase tumor metastasis via angiogenesis

Nitrous Oxide

• Inhibits formation of mononuclear cells
• Depresses neutrophil chemotaxis and function
• Most potent stimulator of lung and liver metastasis of all anesthetic drugs studied (animal studies)

What about Xenon?

Effect of xenon anaesthesia on relapse-free survival in treatment of breast cancer: relation with immune status: 1AP3-4

- Avdeev, S.; Stakheeva, M.; Odyshev, V.; Faltin, V.; Slonimskay, E.
- European Journal of Anaesthesiology: June 2014 - Volume 31 - Issue - p 11
- Evidence-based Practice and Quality Improvement

Studied 60 breast cancer patients on day 1 and day 7 after radical surgery.

- 29 patients who received xenon anesthesia
- 31 patients who received anesthesia with nitrous oxide
- 6-year follow-up period (2005 - 2011).

Conclusion: Analysis of changes in the immune status of patients who received xenon anesthesia showed not only the absence of suppression of cell mediated and humoral immune responses but also the presence of protective effect on the functional activity of neutrophil phagocytes.
Inhaled vs. Propofol

- Amount of apoptosis from patients undergoing breast cancer surgery
- Pre-surgery
- 1 hour post-op

Are all the Opioids the same?

<table>
<thead>
<tr>
<th>Opioids effect on tumor recurrence</th>
<th>Peri &amp; post operative</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td></td>
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<tr>
<td>Codeine</td>
<td></td>
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<tr>
<td>Fentanyl</td>
<td></td>
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<tr>
<td>Hydromorphine</td>
<td></td>
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<tr>
<td>Buprenorphine</td>
<td></td>
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<tr>
<td>Tramadol</td>
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Angiogenesis: Vascular Endothelial Growth Factor

https://selfhacked.com/blog/need-know-vegf-good-bad/
Cyclooxygenase Inhibitors

• Decrease angiogenesis
• Increase tumor apoptosis
• Decrease opioid effects on cancer recurrence

**Ketorolac**

**METHODS:** The main objective was to compare the incidence of breast cancer recurrence among patients who received different analgesics during surgery.

**RESULTS:** Univariate and multivariate analyses showed a lower cancer recurrence rate when ketorolac was given before surgery (P = 0.019). Other analgesics (sufentanil, ketamine, and clonidine) were not associated with a significant reduction in cancer recurrence rates in our series.

**CONCLUSION:** This retrospective analysis suggests that intraoperative administration of ketorolac decreases the risk of breast cancer relapse compared with other analgesics.

Local Anesthetics

- Lidocaine may be suppressing angiogenic potential in some prostate cancer types by decreasing the morphine-induced production of VEGF
- Lidocaine infusions may acquire a distinct clinical application in the perioperative care of prostate cancer patients

Local Anesthetics

- Early evidence indicates that LAs decrease cancer cell migration
- Location, concentration, duration are still unknown.

Local Anesthetics: Regional, Opioid-Sparing

**Background:** PSA levels after surgery
- GA + epidural
- GA + opioid

**Results:** GA + epidural had an estimated 57% lower risk of recurrence compared with the general anesthesia plus opioids group.

Hypothermia and Natural Killer (NK) Activity

- Rats anesthetized with thiopental for 2.5 hours
  - Randomized:
    - Normothermia
    - Hypothermia

Con

• Randomized controlled trial

• No difference in epidural vs. without

## Putting it all together

<table>
<thead>
<tr>
<th>Perioperative factors that may promote metastasis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Chemotherapy side effects</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Immune system depression</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Stress response Exaggerated by SNS stimulation</strong></td>
<td></td>
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<tr>
<td><strong>Pain</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hypothermia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anesthetic Technique</strong></td>
<td></td>
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</tbody>
</table>

### Good
- Versed
- Cox 2
- Regional
- Propofol
- Lidocaine infusion

### Bad
- Opiods
- Volatiles
- Ketamine
- Sterioids
- Alpha 2
- Calcium channel blockers

### Surgical procedure
- Tumor manipulation, stress response

### Hypoxia and hyperoxia
- Bad

### Allogenic blood transfusion
- Bad
Summary

<table>
<thead>
<tr>
<th>Anesthetic agent</th>
<th>Mitogenesis</th>
<th>Angiogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Volatile</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>COX inhibitors</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Local Anesthetics</td>
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</tbody>
</table>

A suggested technique:
- Propofol TIVA
- Regional block
- COX-2 inhibitor
- Ketorolac

Or, more generally:
- Propofol
- COX-2 inhibitor
- Whatever reduces opioid consumption
Vanderbilt Breast ERAS for partial mastectomy with lymphadenectomy or total mastectomy

**Preop**: Gabapentin/Tylenol

**Intraop**
- TIVA with Propofol LMA vs ETT with BIS
- PEC 1 and 2 block with Ropivicaine
- Methadone if opioid dependant
- Hydromorphone 0.5-1mg if necessary
- Toradol

**Post op**
- Gabapentin/Tylenol/motrin/oxycodone +/- tramadol

**PONV**: Zofran, haloperidol, scopolamine, promethazine
The End
References

1. Doe et al. Inhibition of cancer cell proliferation by midazolam by targeting transient receptor melastin 7 (TRPM7). Onco lett 2013. 5(3). 1010-1016.
8. The Role of the Perioperative Period in Recurrence After Cancer Surgery
   Gottschalk, Antje MD*; Sharma, Sonal MD; Ford, Justin MD; Durieux, Marcel E. MD, PhD; Tiouririne, Mohamed MD Anesthesia & Analgesia: June 2010 - Volume 110 - Issue 6 - p 1636–1643