Anesthesia for Cancer Surgery: How we can impact survival

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Cancer in the United States

- National Cancer Institute
  - 2018
    - 1,735,350 new cases
    - 609,640 deaths
- Approximately 38.4% of men/women will be diagnosed with cancer at some point in their life
- 2017 Expenditure: $147.3 billion

Cancer in the United States

We are getting better at treatment!

1990 → 2014 overall death rates decreased 25%

Let’s do more!!
Surgical Oncology

- Surgical excision
  - Best chance of survival for most solid tumors
  - Can be problematic


Surgical Oncology

- Primary tumor uncommonly directly results in patient death
- Most morbidity and mortality is related to recurrence and metastatic spread to other organs
- Minimal Residual Disease (MRD): small number of cancer cells that remain in the body after cancer treatment


Surgical Oncology

- Potential problems with surgical excision
  - Disruption of tumor cells and blood supply at site of excision
  - Surgical Stress
    - Immunosuppression
    - Hypothalamic-pituitary-adrenal axis
    - Sympathetic nervous system
  - Anesthetic agents

Potential tumor seeding + impaired immunity = ↑ susceptibility for metastasis
Perioperative Surgical Oncology

- Multiple factors influence whether residual cancer cells or pre-existing micro-metastases become able to initiate new metastases or are eliminated by the immune system
- Cancer cells evade normal host defenses: NK cells and cytotoxic T-lymphocytes (CTLs)
- Increased blood vessel density at primary tumor site helps to enhance tumor leakage into blood/lymphatic system
- Circulating tumor cells escape from blood and lymphatic vessels
- Colonization/angiogenesis in target organ

Cancer immunity

**PRO TUMOR**
- IL-4, IL-6, IL-10
- M2 macrophages (MDM), TAM, CD4+ Th2

**ANTI-TUMOR**
- IL-2, IL-12, INF-γ, TNF-α
- CD4+ Th1

**Cytotoxicity**
- NK cells
- CD8+ CTLs

**Immunosuppression**
- IL-6, IL-10, VEGF, PGE2
- T-reg cells, TAM, CD4+ Th17

**Cancer cells**
So, what can we do?!?!

Long-term Survival for Patients Undergoing volatile versus IV Anesthesia for Cancer Surgery
A Retrospective Analysis

Shahram Jami, Ph.D., M.R.C.P., F.R.C.A., F.F.I.C.M.

Anesthesiology 2016

- All patients presenting for elective surgery at Royal Marsden Foundation Trust (tertiary comprehensive cancer center) in London, England
- June 2010 – May 2013
- 2 groups
  - TIVA: propofol and remifentanil
  - INHA: volatile inhalation agent (sevoflurane or isoflurane) + bolus opioids
- Excluded if patient received both forms of anesthesia (same surgery or additional procedures)
One year survival: 91.2%
- TIVA: 94.1%
- INHA: 87.9%

Median follow-up: 2.66 years

Overall mortality: 18.5%
- TIVA: 13.6%
- INHA: 24%

After propensity matching and adjustment of known confounding variables:
- Hazard ratio 1.46 (95% CI, 1.29 to 1.66) for death in patients receiving INHA
**Cancer immunity**

![Diagram showing interactions between immune cells and cytokines, indicating cancer immunity and immunosuppression.](image)

**Effect of Propofol and Isoflurane Anaesthesia on the Immune Response to Surgery**


<table>
<thead>
<tr>
<th>Time point</th>
<th>Propofol (n=9)</th>
<th>Isoflurane (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>2.4 (2.0-2.5)</td>
<td>2.6 (2.5-3.1)</td>
</tr>
<tr>
<td>T1</td>
<td>2.4 (2.0-3.1)</td>
<td>2.4 (2.0-3.1)</td>
</tr>
<tr>
<td>T2</td>
<td>2.0 (1.8-2.4)</td>
<td>1.2 (0.9-1.5)</td>
</tr>
<tr>
<td>T3</td>
<td>2.2 (1.9-3.0)</td>
<td>0.9 (0.9-1.4)</td>
</tr>
<tr>
<td>T4</td>
<td>2.2 (1.9-3.0)</td>
<td>0.9 (0.9-1.5)</td>
</tr>
</tbody>
</table>

**Th1/Th2 ratio in patients undergoing craniotomy under propofol or isoflurane anaesthesia. Values are median (interquartile range [range]).**

**Comparison between values before induction of anaesthesia and the mean postoperative values.**

- Th1/Th2 ratio was smaller in the isoflurane group than in the propofol group ($p=0.009$).

**Differential Effects of Propofol and Isoflurane on the activation of T-helper Cells in Lung Cancer Patients**

Ren, XF et al. *Anaesthesia*, 2010 65: 478-482

- 30 patients for elective lobectomy for non-small-cell lung cancer
- 2 groups:
  - Propofol induction + propofol maintenance
  - Etomidate induction + isoflurane maintenance
- CD4+CD28+: Co-stimulatory molecule
- IL-12
- INF-$g$/IL-4
- Cortisol ratio
- Time points:
  - T0: just before induction
  - T1: 10 minutes after induction
  - T2: 1 hour after induction
  - T3: Immediately after stopping anesthetic
  - T4: 1 hour post-op
  - T5: 24 hours post op
Cancer immunity

CD4 Th2
IL-4, IL-6, IL-10
MSC
T reg
CD4 Th0
IL-4
CD4 Th0
IL-10
IL-2
INF-γ
CD4 Th1
IL-2, IL-12,
INF-γ, TNF-α
IL-6, IL-30,
VEGF, PGE2
MDSC
TAM
CD4 Th17
IL-2, IL-12,
INF-γ, TNF-α
IL-6, IL-10

Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study

- 363 patients undergoing MRM
- Exclusion:
  - Missing records
  - Metastatic breast cancer
  - Other breast cancer
  - Bilateral or previous breast cancer
  - Other cancer
  - Refusal of post-op treatment
- 325 patients
  - 173: Propofol: propofol induction and maintenance
  - 152: Sevoflurane: thiopental induction, sevo maintenance
Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study

What’s next??

Pilot studies

- Propofol + paravertebral vs sevoflurane-based anesthetic
  - Significantly less apoptosis of ER-negative breast cancer cells exposed to post-op serum from patients maintained with sevoflurane.
Pilot Studies


- Ongoing prospective, multicenter trial
- Propofol + paravertebral anesthetic vs standard GA (sevoflurane) + opioids
- Assessment of immune cell infiltration in breast cancer tissue
  - Sevoflurane: lower median values for NK cells and CD4 (T helper cells)
  - No difference in CD8 (T suppressor cells) or macrophages

Other areas to explore

- Regional anesthetics
- Opioids
  - MORPHINE!
- Beta blockers
- COX-2 inhibitors

My practice

- Propofol-based anesthetics
- Adjuncts as needed
  - Nitrous oxide
  - Ketamine infusion
  - Dexmedetomidine
Conclusion