Objectives

Mechanistic evidence for regional analgesia and cancer recurrence

Animal evidence that regional analgesia ameliorates tumor progression

Human evidence regarding regional analgesia and cancer recurrence
Causes of Long-term Mortality

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>52%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>17%</td>
</tr>
<tr>
<td>Renal/Liver Failure</td>
<td>5%</td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>4%</td>
</tr>
<tr>
<td>Pulmonary Emboli</td>
<td>2%</td>
</tr>
<tr>
<td>Sepsis/Infection</td>
<td>2%</td>
</tr>
</tbody>
</table>

≈10% one-year mortality in patients ≥65 yrs

Monk, A&A 2005
Cancer Surgery

Cancer recurrence is usually lethal

Surgery remains primary treatment
  • Releases tumor cells into blood stream
  • There is always minimal residual disease

Natural killer (NK) cells are major defense
  • Spontaneously recognize and kill tumor cells

Surgery and anesthesia impair NK Cell function
  • Neuroendocrine stress response to surgery
  • Volatile anesthetics
  • Opioids
Regional Analgesia Protective?

Regional anesthesia & analgesia
- Reduces stress response to surgery
- Reduces or eliminates general anesthetics
- Obviates need for postoperative opioids

All three help preserve NK cell function

Hypothesis:
- Regional anesthesia & analgesia reduces risk of cancer recurrence
Natural Kill Activity

Surgery in Rats

Reduced NK Activity
  • In blood
  • In the spleen

Increased lung metastases

Ben-Eliyahu, Int J Cancer 1999
Anesth Increases Tumor Retention


Moudgil, CJA 1997
Opioids are Immunosuppressant

Central pathway
• Glucocorticoid release

Peripheral pathways
• Reduced NK cell activity
• Impaired antibody production
• Decreased cytokine release

Shavit, Neuroimmunomodulation 2004
Paravertebrals & Breast Cancer

Retrospective analysis of 129 mastectomies for CA
- 50 had combined general & paravertebral analgesia
- 79 had general and morphine analgesia

Exadaktylos, Anesthesiology 2006
Epidurals & Prostate Cancer

Retrospective analysis of 225 prostatectomies for CA

• 102 had combined general & epidural analgesia
• 123 had general and morphine analgesia

Epidurals associated with 57% [17-78%] less recurrence

Biki, Anesthesiology 2008
Retrospective analysis of patients for melanoma surgery
• 52 well-matched pairs

Gottschalk, BJA 2012

P = 0.09
Negative Retrospective Results

Ismail et al: BJA 2010
  • Brachytherapy for cervical cancer
    – 63 neuraxial vs. 69 general anesthesia

Gottschalk et al: Anesthesiology 2010
  • Colectomy for colon cancer
    – 256 epidural vs. 253 general anesthesia

Tsui et al: CJA 2010
  • Epidural analgesia for prostate cancer
    – 49 epidural vs. 50 general anesthesia

Forget et al: EJA 2011
  • Epidural analgesia for prostate cancer
    – 578 epidural vs. 533 general anesthesia

Day et al: BJA 2012
  • Laparoscopic colectomy
  • 107 epidural; 144 spinal; and 173 general alone

Etc.
MASTER Trial Follow-up

Myles, BMJ, 2011

Also negative:
Tsui 2010
Christopherson 2008

Epidural (n=230)
General (n=215)
Summary

Three compelling mechanisms protect NK function
- Reduced surgical stress response
- Decreased need for volatile anesthetics
- Decreased Opioid use

Results in rodents are convincing

Human results equivocal
- Retrospective studies mostly negative
- Only randomized trial negative
  - But small and old

Randomized trials needed — and in progress