Anesthesia for Cancer Surgery

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Introduction: anesthetic technique may affect outcomes for patients with cancer; selection of anesthetic may influence rates of survival and recurrence after surgery and anesthesia

Fried (1977): performed retrospective analysis of end results of therapy in ≈1300 patients with breast cancer; 7 to 10 yr after operation, rate of survival when halothane used found to be 7% to 10% higher than rate observed after use of ether; difference in rates of survival increased with increasing size of tumor; author suggested investigation of anesthetic as factor influencing end results of cancer therapy; data potentially confounded by differences in surgical technique

Cancer rates: projected increase in incidence by 2030 45%; more prevalent than cardiovascular disease among patients aged <90 yr; 1 in 3 people likely to develop cancer; expect 13.1 million cancer-related deaths worldwide by 2030; accounts for 13% of all deaths worldwide; predicted to surpass cardiovascular disease as leading cause of death in developed countries; in men, cancers prevalent during early teenage years and between 50 and 80 yr of age; among women, cancers common early in life and between 40 to 80 yr of age

Most common types of cancer: for men, lung cancer most prevalent (followed by prostate); survivability very poor with cancer of lung and reasonable with cancer of prostate; survival very poor with cancer of pancreas; for women, breast cancer most common, with reasonable survivability; survivability poor with cancer of lung and very poor with cancer of pancreas

Immunoeediting: refers to body’s natural defenses against growth of cancer; innate immune system detects and destroys cancer cells, primarily through natural killer (NK) cells; body normally exists in state of equilibrium (abnormal cells develop and begin to grow but eliminated by immunoeediting); escape phenomenon leads to unrestricted growth or emergence of clinical cancer; carcinogens, radiation, viral infections, chronic inflammation, or genetic mutation can lead to development of intrinsic tumor cells with abnormal antigens

T lymphocytes: progenitor form differentiates into Th1 or Th2; Th1 cells promote formation of cytotoxic lymphocytes and NK cells; Th2 cells form immunosuppressive macrophages that promote angiogenesis and favor growth of tumor

NK cells: effectively eliminate tumors that develop naturally; activity of NK cells measurable; rates of cancer-related mortality greater among patients with low levels of NK cell activity, especially those with fast-growing cancers (eg, colorectal, lung, gastric); NK cells suppressed by inflammation, increased levels of prostaglandins during stress response, and volatile anesthetics

Apoptosis: natural programmed death of abnormal cells; may be increased or decreased by anesthetics

Inflammation: acute inflammation: adaptive immune response to pathogens and abnormal cancer cells; chronic states of inflammation produce tumorigenic environment by increasing cellular proliferation, growth of blood vessels into tumor, and invasion of tissue by tumor

Angiogenesis: progression of blood vessels into tumor facilitates distribution of abnormal cells to other parts of body; abnormal cells penetrate blood vessels to establish metastatic foci

Perioperative factors: major surgery causes damage to tissues; psychological stress and anesthetic factors also affect tumor

Surgical factors: include direct trauma to tissue and release of residual disease or circulating tumor cells; preoperative reduction in size of tumor important to minimize residual disease and release circulating tumor cells (to reduce the likelihood of local and metastatic recurrence); surgical technique may affect recurrence; direct trauma causes dilation of lymphatic system and increases levels of vascular endothelial growth factor, μ-opioid receptor, matrix metalloproteinase, cyclooxygenase (COX), and prostaglandins, all of which stimulate tumor growth

Modifiable factors: stress related to surgery increases NK, interleukin, and inflammatory activity, which increase growth of tumor cells and survival of metastatic cells in vitro and in vivo; suppression of immune system should be minimized

Anesthetic factors: opioids, volatile anesthetics, blood transfusions, hypothermia, and hypoxemia suppress immune system; animal data clearly indicate that morphine induces immunosuppression; opioids can have proangiogenic effects; early published studies suggest agents that block effects of opioids improve survival

Schlagenhauff et al (2000): performed registry review of ≈4000 patients who underwent excision of melanoma under local or general anesthesia; found higher survival rate at 120 mo for patients receiving local vs general anesthetic; because authors did not control for size of tumor or choice of anesthetic, speaker questions conclusion that general anesthesia negatively affects survival

Immunosuppression: studies demonstrate immunosuppressive activity of thiopental, ketamine, and volatile anesthetics; general anesthesia and related perioperative stress cause depression of immunocompetent cells and signaling cascades

Educational Objectives

The goals of this program are to improve the management of anesthesia for cancer surgery and the minimally invasive management of eyelid malposition. After hearing and assimilating this program, the clinician will be better able to:

1. Interpret current literature about the effect of anesthetic agents on cancer outcomes
2. Minimize perioperative suppression of the immune system
3. Use multimodal anesthetic techniques to minimize the risk for cancer recurrence
4. Consider the impact of regional vs general anesthesia on the recurrence of cancer
5. Review minimally invasive techniques that delay or avoid the need for surgery on the eyelid

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Goldberg presents information related to the off-label or investigational use of a therapy, product, or device.
Lindholm et al (2014): in cohort of 766 patients, found neither duration of anesthesia nor cumulative time of profound anesthesia with sevoflurane increased risk for new cancer or death within 5 yr of surgery

**Protective effects of anesthetic agents:** propofol inhibits COX and catecholamines; local anesthetics directly stimulate NK cells and preserve balance between Th1 and Th2 cells; several papers suggest total intravenous anesthesia with propofol or regional block preferred, and use of opioids should be minimized

**Volatile anesthetics:** associated with increased recurrence of tumor in animal models; inhaled anesthetics upregulate hypoxia-inducible factor, which can facilitate spread of cancer in animals; general anesthesia combined with regional anesthesia appears to improve immune outcome and reduce metastatic burden in animals (no prospective randomized trials in humans)

Buckley et al (2014): compared effects of propofol vs inhalational anesthetic on NK cell activity using serum obtained from 10 participants preoperatively and 24 hr after surgery for breast cancer; NK activity decreased in group receiving inhalational anesthetic; study not randomized; authors advise against use of volatile anesthetics and opioids

Gupta et al (2002): at clinical doses, morphine stimulates angiogenesis in xenograft mouse model of human breast cancer; morphine also accelerates tumor progression

Smith et al (2002): randomized 200 participants with refractory pain caused by cancer to implantable device (plus low-dose opioids) or systemic high-dose opioids; found longer survival in patients with implanted devices

Morphine: clinically relevant doses accelerate tumor growth and decrease survivability in transgenic mice; increases tumor angiogenesis, peritumoral lymphangiogenesis, and activation of mast cells; blocks apoptosis and decreases activity of NK cells

Exadaktylos et al (2006): performed retrospective study of 129 patients who underwent mastectomy and axillary clearance and received paravertebral block with general anesthesia or general anesthesia with postoperative morphine; found decreased recurrence and metastasis at 36 mo in patients who underwent paravertebral block; patients in general anesthesia group had slightly larger tumors, smaller margins, and higher rates of chemotherapy (groups not comparable); no information provided about amount of morphine or type of chemotherapy administered; speaker considers paper as hypothesis, not conclusion

Additional studies: one study found no statistical difference between epidural with light general anesthesia and general anesthesia alone; Scavonnet et al (2014) found statistically less systemic progression, death from prostate cancer, and death from any cancer in patients who received neuraxial blockade in addition to general anesthesia; additional studies showed no difference between general and regional anesthetic

Sprung et al (2014): compared general with epidural anesthesia (bupivacaine plus fentanyl) in 486 patients undergoing prostatectomy, and found no difference in outcomes; however, epidural contained high quantities of fentanyl and therefore did not allow for systemic opioid-sparing effect

**Retrospective reviews:** suggest higher rates of recurrence and shorter survival with volatile anesthetics vs total intravenous anesthesia; appear to favor multimodal analgesia; Maher et al (2014)—found lower rate of recurrence at 5 yr with lower doses of opioids among ≤100 patients with cancer of lung (prospective randomized trial under way to confirm association)

**µ-opioid receptors:** increased expression in patients with metastatic lung cancer; stimulate angiogenesis and progression of tumor; inhibition of µ-receptors effective in animal models

**Anti-inflammatory agents:** exert anti-metastatic and anti-proliferative effects (particularly COX-2 inhibitors); COX inhibitors decrease growth and activity of tumor in vitro and in vivo; Retsky et al (2012) found reduction in recurrence of breast cancer associated with administration of ketorolac; Forget et al (2014) found improved outcomes with nonsteroidal anti-inflammatory drugs

**Statins:** maintain balance between Th1 and Th2 mediators of inflammation, and C-reactive protein; may have anticancer properties in certain animal models

**β-blockers:** associated with decrease in rate of recurrence of cancer (mechanism [blood pressure vs reduction of stress] unclear); retrospective review by Powe et al (2010) found better outcomes in patients taking β-blockers

**Additional factors:** hypothermia—causes stress and leads to suppression of immune function; blood transfusions—increase recurrence of cancer; aspirin—associated with decreased rates of recurrence; Rothwell et al (2012) performed analysis of 51 trials and found decreased incidence of recurrence among patients who had taken aspirin for ≥5 yr but no change in rates of cancer during first 3 yr; found increased risk for bleeding during first 3 yr; oxygen—data mixed; immunotherapy—several trials assessing specific antioxidants suggest decrease in adverse events; exercise—active patients have lower recurrence rates and better survival

**Suggested Readings**


Minimally Invasive Management of Eyelid Malposition and Asymmetry

Robert A. Goldberg, MD, Karen and Frank Dabby Professor of Ophthalmology, Chief, Orbital and Ophthalmic Plastic Surgery Division, Director, Orbital Disease Center, and Co-Director, Aesthetic Center, Jules Stein Eye Institute, University of California, Los Angeles

Lower eyelid retraction: shortening of middle lamella of eyelid plays role; loss of volume likely more important; leads to
strategy of reinflating, as opposed to lengthening, eyelid; dermis harvested to replace volume; strip of dermis placed through minimal incision using Keith needle

**Hyaluronic acid gels:** approved by US Food and Drug Administration >10 yr ago; multiple brands available; viscoelastics cross-linked by chemical process to prevent digestion by endogenous hyaluronidase (can last ≤5 yr)

**Case examples:** 1) patient with complicated lower-eyelid retraction received 2 layers of hyaluronic acid gel; function improved dramatically; 2) patient with tight eyelid, weak orbicularis muscle, and exposed conjunctiva after blepharoplasty; chemosis subsided 3 wk after placement of hyaluronic acid gel; although scar tissue cannot be transformed into normal tissue, nonsurgical treatments can reinflate area and reform canthal angle cosmetically and functionally; 3) patient with congenital ichthyosis (nonsurgical problem); various papers propose different strategies for grafts, none of which prevent reconstruct; speaker placed intradermal hyaluronic acid gel within dermis to stretch tissue, with resulting preservation of vision in patient’s left eye (patient followed for ≥6 yr)

**Upper eyelid retraction:** seen frequently (eg, thyroid orbitopathy); injections performed in levator plane; all uses of medicament in presentation off-label, but speaker considers risk low; technique used for 10 yr; useful for patient with acute thyroid orbitopathy in early stages of disease, when path of progression unclear; immediate surgery undesirable because retraction may resolve spontaneously; placing hyaluronic acid gel in levator plane provides cosmetic and functional improvement lasting ≤1 yr; treatment with hyaluronic acid gel helps patients during unstable phase of disease; need for surgery assessed after disease stabilizes

**Facial palsy:** observed when levator muscle functions but orbicularis does not; baseline retraction present; lagophthalmos develops and eyelid unable to close; addition of weight and possibly volume in levator aponeurosis through application of hyaluronic acid gel allows eye to close; good option for patient with recent onset of facial palsy for whom return of function possible

**Congenital ectropion and retraction:** threatens cornea; surgery challenging in infants; possible to inject hyaluronic acid into levator and subcutaneous planes in neonatal intensive care unit; provides temporary improvement; additional intervention may be required, or condition may resolve

**Orbital rim hollow:** cosmetic issue; aesthetic surgery for eyelids often addresses “puffy” eyelids; standard techniques for tissue removal effective for true puffy eyelids; aging involves hollowing of eyelid; paradigm for rehabilitation changing to focus on addition of volume (eg, eyelid rim, zygomatic hollows in superior and inferior orbit); in speaker’s experience, results typically better with filling than with surgery; similar principles apply to superior sulcus hollow

**Suggested Readings**


**Acknowledgments**

Dr. Leslie was recorded at Scottsdale Anesthesia, held October 8-14, 2016, in Scottsdale, AZ, and presented by Holiday Seminars. For information about upcoming CME opportunities from Holiday Seminars, please visit holidayseminars.com. Dr. Goldberg was recorded at the 30th Annual Scientific Meeting of the Ophthalmic Anesthesia Society, held September 9-11, 2016, in Chicago, IL, and presented by the Ophthalmic Anesthesia Society. For information about upcoming CME opportunities from the Ophthalmic Anesthesia Society, please visit eyeanesthesia.org. The Audio Digest Foundation thanks the speakers and sponsors for their cooperation in the production of this program.

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**Estimated time to complete the educational process:**

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<td>Review Educational Objectives on page 1</td>
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ANESTHESIA FOR CANCER SURGERY/MANAGEMENT OF EYE ISSUES

To test online, go to www.audiodigest.org and sign in to online services.
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1. Which of the following is the most prevalent type of cancer in men?
   (A) Lung  (B) Pancreatic  (C) Prostate  (D) Colorectal

2. Which of the following is the most prevalent type of cancer in women?
   (A) Lung  (B) Pancreatic  (C) Breast  (D) Cervical

3. Which of the following cell types promotes the formation of natural killer cells?
   (A) Th1  (B) Th2  (C) Macrophages  (D) Plasma cells

4. Rates of cancer-related mortality are greater in patients with ______ natural killer (NK) cell activity. Volatile anesthetics ______ NK cells.
   (A) High; stimulate  (B) High; suppress  (C) Low; stimulate  (D) Low; suppress

5. All the following have been shown to suppress the immune system, EXCEPT:
   (A) Opioids  (B) Thiopental  (C) Local anesthetics  (D) Ketamine

6. Which of the following compounds has been shown to increase the rate of cancer recurrence?
   (A) Ketorolac  (B) Nonsteroidal anti-inflammatory drugs  (C) β-blockers  (D) None of the above

7. In an analysis of 51 trials conducted by Rothwell et al (2012), which of the following was observed among patients taking daily aspirin?
   (A) Decreased incidence of cancer during the first 3 yr of aspirin use  
   (B) Increased risk for bleeding during the first 3 yr of aspirin use  
   (C) No effect on rates of cancer recurrence after taking aspirin ≥5 yr  
   (D) No statistically significant effects on rates of cancer or bleeding

8. Hyaluronic acid gel is injected in the ______ plane for the treatment of upper eyelid retraction.
   (A) Levator  (B) Subcutaneous  (C) Dermal  (D) Suborbital

9. Which of the following scenarios results in facial palsy?
   (A) Levator muscle function is intact and orbicularis muscle function is absent  
   (B) Levator muscle function is absent and orbicularis muscle function is intact  
   (C) Function is absent in the levator and orbicularis muscles

10. All of following statements about the use of hyaluronic acid for the treatment of congenital ectropion and retraction are true, EXCEPT:
    (A) Involves injection into the levator plane  
    (B) Involves injection into the subcutaneous plane  
    (C) Can be performed in the neonatal intensive care unit  
    (D) Provides a permanent solution

NOTE: The correct answers to Audio Digest Anesthesiology Volume 58, Issue 43 are as follows:
1-C, 2-B, 3-A, 4-C, 5-C, 6-B, 7-A, 8-B, 9-A, 10-B

Answers to Audio Digest Anesthesiology Volume 59, Issue 03: 1-B, 2-D, 3-A, 4-D, 5-C, 6-A, 7-D, 8-B, 9-B, 10-A