

Anesthesiologists, Anesthetics, and Cancer metastasis

Onco-anesthesia remains challenging in view of issues related to major surgical procedures, associated impact of concomitant cancer therapy like chemotherapy, radiotherapy, and co-morbidities. Curative surgical resection is the mainstay treatment modality for potentially curable solid tumors. Surgery is associated with body stress response, which have metabolic, neuroendocrine, hematological, and inflammatory/immunological responses (cytokine stress responses, suppressed cell-mediated immunity).^[1-3] These are the major factors for perioperative immune suppression and provide a milieu for possible tumor cell proliferation leading to metastases.^[1-6] Other surgical factors include residual minimal disease and dissemination of tumor cells during surgery.^[3,6] The impact of pain, blood transfusion, hypothermia, hypoxic episodes, organ hypoperfusion, hyperglycemia, anesthetic drug, and technique for cancer recurrence has been reported.^[7-9] These adverse response during curative surgical management requires perioperative physicians, including anesthesiologists, surgeons, and oncologists, to maintain homeostasis against the consequences of both cancer and tissular attrition.^[10] The balance between the metastatic potential of the tumor and the anti-metastatic host defenses is the decisive factor for the risk of metastasis.^[11,12]

Data is being increasingly published related to possibility of cancer recurrence or metastasis by certain anesthetics or anesthetic techniques. The anesthetic management influence immunity and possibility of cancer recurrence by effect on cellular mechanisms (e.g. cell apoptosis) or influence on the endocrine and sympathetic systems.^[10] This issue is accompanied with an review article wherein the authors have reviewed the impact of anesthesia-related effects on cancer recurrence.^[13]

Anemia is seen in surgical patients in the range of 5% to 75%.^[1,2] This appears to be more prevalent in onco-surgical patients in view of adverse effects of concomitant chemo-radiotherapy in addition to disease-related inadequate

nutritional intake. The baseline hemoglobin is the most important predictor of blood transfusion in surgery.^[2] On one hand, the preoperative anemia is an independent predictor of increased postoperative morbidity and mortality while on the other hand, blood transfusion-related adverse effects like transmissible infectious agents, transfusion reactions, and effects on immunomodulation like tumor progression are well-known.^[1,2] This immunomodulation by blood transfusion may increase the risk of recurrence or increase possibility of metastasis. These issues create a dilemma in perioperative management of onco-surgical major surgical procedures regarding triggers for blood transfusion. The options available then include autologous transfusion and better nutritional optimization prior to surgical intervention. The roles of nutritional optimization by home-based supplements are well described but may be a concern in onco-surgical procedures in view of urgency of the surgery. The oral and/or parenteral nutrition in the perioperative period improves the immunity and thus may be beneficial for onco-surgical patients.^[14] The role of parenteral nutrition including supplements of minerals and vitamins and role of erythropoietin which has been described as ‘patient-centered blood management’ needs to be assessed.^[15] Thus, in major oncological procedures, attempts needs to be made to optimize the patient’s hemoglobin, reducing perioperative blood loss and thus lesser blood transfusion.^[15] Also, some evidence exists for the propensity of tumor-promoting effects by stored blood and old erythrocytes.^[14] The release of various mediators which is proportional to the stored age of the blood products leads to immunosuppression and tumor-promoting action.^[14] Though it appears logical that leucodepleted blood would induce less immune suppression and thus lesser risk of cancer recurrence, use of leucodepleted blood for preventing cancer recurrence has conflicting reports.^[14,16] The risk of recurrence may also be related to volume of blood transfused, which increases with the more transfusions.^[14] The timing of blood transfusion with regards to surgical intervention has been associated with the cancer recurrence. The pre-, intra-, and post-operative blood transfusion increases the risk of cancer recurrence by 50%, 74%, and 36%, respectively.^[14] Though these data indicates transfusion of blood products in large quantity, older stored non-leucodepleted blood, increases the possibility of cancer recurrence, but further clinical trials are still required to confirm these findings.^[14]

Hypothermia in the perioperative period has deleterious effect on the patient. Hypothermia impairs immunity by impairing the

Access this article online	
Quick Response Code:	Website: www.joacp.org
	

function of neutrophils and cytokine and antibody production.^[5,14] Also, hypothermia causes coagulopathy and increases chances of blood transfusion and thus risk of immunomodulation.^[14] In fact, thermotherapy (applied locally, regionally, and systemically) has been used as a part of multimodal therapies to various tumors.^[17] The hyperthermic chemotherapy infused intra-peritoneally is a known procedure for prevention of cancer recurrence in certain tumors.^[5,17] Hence, perioperative hypothermia needs to be prevented in onco-surgical procedures to reduce risk of cancer recurrence.^[14]

Various techniques of anesthesia have an impact on the cancer recurrence. With the availability of better airway gadgets like supraglottic airway devices and anesthetic drugs (faster, shorter acting like remifentanyl, propofol, sevoflurane, desflurane, etc.) the anesthetic technique for some surgical procedures has drifted away from regional blocks. But, the potential benefit for regional anesthesia in oncologic patients with regards to decreased cancer recurrence following oncologic surgery have been reported.^[7] Hence, it appears that we need to have an evidence based anesthetic technique for the cancer and non-cancer surgical procedures.^[3]

The premedication has to be improvised for onco-surgical procedures in view of beneficial effect of certain drugs. Certain cancer cell types have increased expression of COX-2 and thus may have preventive action on cancer recurrence perioperatively.^[18] Also, preemptively administered non-specific COX-inhibitor ketorolac has been reported to reduce cancer recurrence after surgery for breast cancer.^[18] The COX-2 inhibitors also prevent the dilation of lymphatic systems perioperatively and thus lesser risk of tumor cell spread.^[8] It has been reported that immunosuppressive and metastatic potential of ketamine may be prevented by pre-administration of β -blockers by its effect of attenuation of the immunosuppressive and prometastatic effects of ketamine anesthesia.^[8,19] It has been reported that β -blockers reduced the risk of metastasis by 57% in patients of breast cancer.^[14] It has been studied in an animal model that β -blockers and COX-2 inhibitors synergistically attenuate perioperative immune suppression and the metastasis-promoting effects during the surgical intervention.^[8,20] Thus, it has been proposed that β -blockers reduce the surgical stress response and thus act as an anti-metastatic agent.^[8] Similarly, statins have preventive effects on tumor metastasis.^[8] So, it appears that for the patients undergoing onco-surgical procedures, the conventional premedication may be modified to include β -blockers, COX-2 inhibitors, statins, steroids, especially glucocorticoids, and immunotherapy. Also, certain agents being used as adjuncts to anesthetic agents like α_2 agonists like clonidine and dexmedetomidine may lead to tumor progression in certain cell types and thus need to be used cautiously in

oncologic surgical procedures. In addition, midazolam also impairs immune response and poses a risk of tumor recurrence and hence may be avoided for premedication.^[14]

The published literature relating to the cancer recurrence and anesthesia has limitations. Majority of published data are underpowered, non-randomized, retrospective, or having some confounding variables known to cause cancer recurrence. Though the evidence is still not very robust for any specific anesthetic technique for onco-surgical procedures, we need to be careful in choosing the technique drugs based on available evidence to avoid any risk of cancer recurrence or metastasis.^[3] The available data suggests the total intravenous anesthesia with propofol, cyclooxygenase antagonists, and regional anesthesia can decrease negative consequences associated with perioperative immunosuppression while volatile anesthesia, systemic morphine administration, unnecessary blood transfusions, intraoperative hypoxia, hypotension, hypothermia, and hyperglycemia should be avoided.

Rakesh Garg

Department of Anesthesiology, Pain and Palliative Care,
Dr. Brairch, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Dr. Rakesh Garg,
35, DDA Flats, East Punjabi Bagh, New Delhi - 110 026, India.
E-mail: drrgarg@hotmail.com

References

1. Goodnough LT, Shander A. Patient blood management. *Anesthesiology* 2012;116:1367-76.
2. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, *et al.* Red blood cell transfusion: A clinical practice guideline from the AABB. *Ann Intern Med* 2012;157:49-58.
3. Tsui BC, Green JS. Type of anaesthesia during cancer surgery and cancer recurrence. Regional anaesthesia has short term benefits over general anaesthesia, but cancer related effects are unknown. *BMJ* 2011;342:1605.
4. Shakh G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: Could they reduce recurrence rates in oncological patients? *Ann Surg Oncol* 2003;10:972-92.
5. Bauer M, George JE 3rd, Seif J, Faraq E. Recent Advances in epidural analgesia. *Anaesthesiol Res Pract* 2012;2012:309219.
6. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: A retrospective analysis. *Anesthesiology* 2008;109:180-7.
7. Missair A, Gebhard RE. Cancer Recurrence and Anesthetic Technique: A "Wake Up Call". *Int J Clin Anesthesiol* 2013;1:1005-6.
8. Ismail H, Hiller J. Cancer recurrence, perioperative interventions and anaesthesia: Review of current evidence. *Sri Lanka J Anaesthesiol* 2012;20:68-72.
9. Kurosawa S. Anesthesia in patients with cancer disorders. *Curr Opin Anaesthesiol* 2012;25:376-84.
10. Forget P, Simonet O, De Kock M. Cancer surgery induces inflammation, immunosuppression and neo-angiogenesis, but is it influenced by analgesics? *F1000Res* 2013;2:1-8.

11. Quan C. Regional Anaesthesia: The A, B and Cs. *S Afr Fam Pract* 2013;55:32-5.
12. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: Could they reduce recurrence rates in oncological patients. *Ann Surg Oncol* 2003;10:972-92.
13. Das J, Kumar S, Khanna S, Mehta Y. Are we causing the recurrence-impact of perioperative period in long term cancer prognosis: Review of current evidence and practice. *J Anaesth Clin Pharmacol* 2014;30:153-9.
14. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. *Br J Anaesth* 2013;110:690-701.
15. Spahn DR, Theusinger OM, Hofmann A. Patient blood management is a win-win: A wake-up call. *Br J Anaesth* 2012;108:889-92.
16. Fergusson D, Khanna MP, Tinmouth A, Hebert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: Two metaanalysis of randomized controlled trials. *Can J Anesth* 2004;51:417-24.
17. Schmidt C, Creutzenberg M, Piso P, Hobbhahn J, Bucher M. Perioperative anaesthetic management of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Anaesthesia* 2008;63:389-95.
18. Bovill JG. Surgery for cancer: Does anesthesia matter? *Anesth Analg* 2010;110:1524-6.
19. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: Direct and indirect effects of anesthetic agents. *Int J Cancer* 2012;130:1237-50.
20. Benish M, Ben-Eliyahu S. Surgery as a double edged sword: A clinically feasible approach to overcome the metastasis promoting effects of surgery by blunting stress and prostaglandin responses. *Cancers (Basel)* 2010;2:1929-51.

How to cite this article: Garg R. Anesthesiologists, Anesthetics, and Cancer metastasis. *J Anaesthesiol Clin Pharmacol* 2014;30:174-6.
Source of Support: Nil, **Conflict of Interest:** None declared.

Author Help: Reference checking facility

The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. *Otolaryngol Head Neck Surg* 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.