Anesthesia's Role in Cancer Recurrence

Most deaths due to cancer result from the growth of metastases originating from a selected subpopulation of malignant cells residing in a primary tumor. These cells are the product of a process mediated by our own immune system referred to as Immunosurveillance and Immunoediting. Surgical excision of these cells improves prognosis in patients with solid tumors at the cost of increasing metastatic risk. There is increasing evidence suggesting anesthetic techniques may play a role in both our immune system's response to malignant cells and in reducing tumor metastases (1, 2).

The Immunosurveillance and Immunoediting theory states that malignant cell populations undergo three phases of growth prior to spreading. In the initial elimination phase, malignant cells penetrate past basement membranes into vascular endothelium. This process elicits an inflammatory response which activates the innate immune system and eliminates malignant phenotypes. Consequently, the immune system molds the immunogenic phenotypes of malignant cells that do survive. The period of immune-mediated latency after incomplete tumor destruction is known as equilibrium. During this period, there is a balance between malignant cell population growth and its elimination. Escape refers to the final outgrowth of tumors that overcome the immune system and outgrow the equilibrium phase in order to metastasize.

Prior to the process of escape, surgical excision offers a good prognosis in patients with solid tumors. However, surgery can increase the risk of metastasis by spreading tumor microemboli and increasing expression of pro-angiogenic factors that aid in tumor growth such as vascular endothelial growth factor (VEGF) (3, 4). In fact, the postoperative presence of neoplastic cells in circulation has been associated with shorter disease free survival rates of human colorectal cancers (5). The surgical stress response has been connected to immunosuppression through mechanisms that include attenuation of natural killer cell function implicated in malignant cell targeting. Additionally, hypothermia and allogenic blood transfusions have been associated with immunosuppression, increased risk of cancer recurrence and reduced survival.

Surprisingly, the anesthetic management of the cancer patient may have an effect on long term survival without metastasis. Local anesthetics (LA's) such as lidocaine have been shown to reduce tumor growth factor secretion in vitro. Additionally, they have been implicated in the inhibition of transcription pathways related to neoplasia and metastasis and reactivation of tumor suppressor genes. Voltage-gated sodium channels similar to the ones LA's block have been shown to enhance metastatic cell behaviors, such as lateral motility and invasion in solid tumors (6, 7). Current evidence points towards regional anesthesia and anesthetic techniques that reduce overall opioid utilization as superior alternatives for cancer survival after excision of solid tumors.

Of the drugs most commonly used in anesthesia, opioids are strongly implicated in cancer recurrence. Although studies on the effect of opioids on immune function and tumor growth are conflicting, opioids have been shown to inhibit components of both cell-mediated and humoral immunity (8). Morphine has been shown to stimulate tumor cell migration and proliferation in human endothelial cells in vitro through VEGF expression. Moreover, exposure of colon carcinoma cells to morphine was associated with a significant increase in secretion of urokinase plasminogen activator suggesting a potential association between morphine and the invasive properties of the tumor (9). Perhaps the strongest evidence implicating opioid use with cancer recurrence stemmed from a study involving methylnaltrexone-a peripheral acting mu receptor antagonist-in the incidental prolonged survival of terminal cancer patients receiving it for constipation (10).

Several retrospective human trials have demonstrated improved outcomes when regional anesthesia is used as opposed to general anesthesia (GA) with IV opioids. In Mastectomy and Axillary Clearance, GA with analgesic paravertebral block showed a 4-fold decrease in cancer recurrence for analgesia when compared against general anesthesia with opioids (11).

In studies involving GA with thoracic epidural vs GA with opioids and NSAIDs a 57% reduction in prostate-specific antigen and increase in progression free survival was noted in the thoracic epidural group (12). When comparing epidural analgesia with GA and opioid analgesia in laparotomy for ovarian carcinoma, an improvement in 3 and 5-year survival rates was noted for the epidural group. Similar observations were made with colorectal surgery (13, 14).

Not all studies were as promising. No difference in recurrence between regional anesthesia and GA were observed for cervical cancer surgery or radiofrequency ablation of prostate carcinoma. Moreover, the perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomized trial observed similar recurrence and recurrence-free survival in the epidural and the GA groups (15).

Further elucidation with prospective trials is required to establish the exact benefits of regional anesthesia over stand-alone GA in tumor resections. Variability in results may be due to ample diversity of tumor phenotypes and staging as well as surgical interventions. Whether these benefits are the result of local anesthetic function or of opioid reduction in

the perioperative period remains to be elucidated. As of now evidence seems to point to the benefits of regional anesthesia in several solid tumor subgroups, particularly those involving surgical interventions for breast, colorectal and prostate cancers (16, 17).

The author/s has/have no conflict/s of interest to disclose.

Manuel Torres-Grajales, MD, PGY-2; **Myrna Morales-Franqui**, MD, DABA, Chairman & Residency Program Director; **Hector Torres-Perez**, MD, DABA, Director of Clinical Research, Department of Anesthesiology, University of Puerto Rico Medical Sciences Campus, San Juan, PR
Email: hector.torres18@upr.edu

References

1. Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. Adv Immunol 2006;90:1-50.
2. Talmadge JE, Fidler IJ. AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 2010; 70: 5649–5669.
3. Heaney A, Buggy DJ. Can anaesthetic and analgesic techniques affect cancer recurrence or metastasis?. Br J Anaesth 2012;109 Suppl 1:i17-i28.
4. Looney M, Doran P, Buggy DJ. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor beta in women undergoing anesthesia and surgery for breast cancer. Anesthesiology 2010;113:1118–1125.
5. Lloyd JM, McIver CM, Stephenson SA, Hewett PJ, Rieger N, Hardingham JE. Identification of early-stage colorectal cancer patients at risk of relapse post-resection by immunobead reverse transcription-PCR analysis of peritoneal lavage fluid for malignant cells. Clin Cancer Res 2006;12:417–423.
6. Sakaguchi M, Kuroda Y, Hirose M. The antiproliferative effect of lidocaine on human tongue cancer cells with inhibition of the activity of epidermal growth factor receptor. Anesth Analg 2006;102:1103–1107.
7. Lucchinetti E, Awad AE, Rahman M, et al. Antiproliferative effects of local anesthetics on mesenchymal stem cells: potential implications for tumor spreading and wound healing. Anesthesiology 2012;116:841–856.
8. Colvin LA, Fallon MT, Buggy DJ. Cancer biology, analgesics, and anaesthetics: is there a link? Br J Anaesth 2012;109:140–143.
9. Gach K, Szemraj J, Fichna J, et al. The influence of opioids on urokinase plasminogen activator on protein and mRNA level in MCF-7 breast cancer cell line. Chem Biol Drug Des 2009;74:390–396.
10. Lennon FE1, Moss J, Singleton PA. The μ-opioid receptor in cancer progression: is there a direct effect? Myles PS, Peyton P, Silbert B, et al. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ 2011;342:d1491.
11. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006;105:660–664.
12. 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;109:180–187.
13. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth 2011;106: 814–822.
14. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective analysis of the effect of postoperative analgesia on survival in patients after laparoscopic resection of colorectal cancer. Br J Anaesth 2012;109: 185–190.
15. Chen WK, Miao CH. The effect of anesthetic technique on survival in human cancers: a meta-analysis of retrospective and prospective studies. PLoS One 2013;8:e56540.
16. American Cancer Society. Cancer Facts and Figures 2012. Available at : Url: http://www.cancer.org/research/cancerfactsfigures/cancer-facts-figures-2012. Accessed 26 February 2016.
17. Kurosawa S. Anesthesia in patients with cancer disorders. Curr Opin Anaesthesiol 2012;25:376–384.