Regional Anesthesia-Analgesia

Relationship to Cancer Recurrence and Infection

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KEYWORDS

• Regional anesthesia • Epidural • Cancer • Infection

KEY POINTS

- Perioperative immune function is important for the development of cancer recurrence and surgical site infection.
- Use of regional anesthesia-analgesia (with a local anesthetic-based regimen) as part of a multidisciplinary approach may attenuate perioperative immunosuppression and provide the physiologic basis for decreasing cancer recurrence and surgical site infection.
- Currently available data examining the relationship between regional anesthesia-analgesia and decreasing cancer recurrence or surgical site infection do not provide any definitive answers due in part to the heterogeneous nature of cancer studied and the limited (methodologic) nature of the studies currently published.
- Although most data are published on nonorthopedic surgical patients, the general principles are similar and can be applied to orthopedic surgical patients.

INTRODUCTION

Patients undergoing surgical procedures will exhibit a transient period of immunosuppression that may provide the permissive circumstances for cancer recurrence or surgical site infections (SSIs). Use of regional anesthesia-analgesia, especially when using a local anesthetic-based regimen, can preserve perioperative immune function and provide the physiologic basis for decreased cancer recurrence and SSI, especially when used as part of a multidisciplinary approach. Although there is little direct

No disclosures.
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Anesthesiology Clin 32 (2014) 841–851
http://dx.doi.org/10.1016/j.anclin.2014.08.004 **anesthesiology.theclinics.com**
1932-2275/14/$ – see front matter

evidence or data investigating orthopedic patients, the basic concepts of the immune system and cancer recurrence/infection are reviewed, which are applicable to all patients, including those undergoing orthopedic procedures, and the available peer-reviewed publications examining the relationship between regional anesthesia-analgesia and these outcomes.

THE IMMUNE SYSTEM AND CANCER

The hypothesis that the immune system is responsible for cancer elimination and suppression is not new.[1] Individuals with suppressed immune systems, such as those with human immunodeficiency virus or requiring immunosuppressive agents after organ transplantation, show increased risks of cancer development.[2–4] A properly functioning immune system is vital in reducing cancer occurrence for the individual. However, the interplay between the immune system and cancer cells is complex and has led to the development of the theory of "immunoediting."

The concept of immunoediting involves 3 phases.[1] The first phase is elimination. This elimination phase entails cells of the innate and adaptive immune system seeking out and eliminating cancer cells. Evidence suggests that individuals with increased natural cytotoxic activity have decreased cancer risk.[5] However, despite this effort at tumor cell control, elimination is not always successful (ie, cancer cells are heterogeneous, and some cancer cells are more susceptible to being killed than others, similar to the concept of antibiotic resistance), leading to the second "equilibrium" phase.[1] In the equilibrium phase, the cancer cells are held in check by the immune system and cancer cells that display decreased immunogenicity are selected, subsequently leading to the third phase of "escape." In this phase, the cancer cells that are more successful at escaping the immune system can result in metastatic tumors.[1]

SURGICAL STRESS LEADS TO IMMUNOSUPPRESSION VIA STRESS RESPONSE

Once tumors are present, surgical excision is often offered as a major treatment option. However, surgery is not often curative because minimal residual disease, either at the tumor margins or at micrometastases at distant sites, can be present. Surgery may actually increase growth in previously unrecognized micrometastases and create an environment that promotes further metastatic spread.[6] As these remaining cancer cells continue to divide, the cellular immune response is often weakened within hours of surgery and lasts for days.[7] This temporary immunosuppression is a result of the neuroendocrine-mediated and cytokine-mediated stress response to surgery. As cellular immunity (an important component of which includes natural killer cells) decreases, cancer morbidity then increases.[8,9] Greater surgical trauma leads to greater suppression of the cellular immune system.[7] In a mouse model, increasing surgical stress leads to a direct increase in metastases.[10] Laparoscopy, which is less invasive than open resection of colorectal cancer, has been shown to be associated with both increased disease-free time and increased time to recurrence.[11] Thus, as surgical stress decreases the immune response, a window period is created that appears to give cancer cells an opportunity to spread. Although surgical stress is an important component, pain can also play a role in immunomodulation.

Pain, much like surgery, can incite the stress response and lead to immunosuppression. Acute pain has been shown to decrease cellular immunity and potentially lead to tumor promotion.[12] How that pain is managed in the perioperative period can have