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EDITORIAL

Regional Analgesia Does Not Reduce Cancer Recurrence. Case closed

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Cancer is the second-leading cause of death worldwide. The initial treatment for nearly all solid cancers is surgical resection of a primary tumor. While tumors can usually be grossly removed, surgical interventions release tumor cells into the lymphatics and vascular beds[1]. Whether circulating tumor cells develop into clinical metastases depends largely on host defense, mostly natural killer cell function[2,3].

Surgery and opioids have the potential to shift the disease-patient relationship towards cancers via at least three major avenues. One is the surgical intervention itself that depresses cell-mediated immunity, reduces concentrations of anti-angiogenic factors, and increases pro-angiogenic factors and release of growth factors that stimulate cancer cells[1,3-8]. Another factor is general anesthesia, which impairs the function of several immune cells important for anti-metastatic immune activity[9]. A third factor is the use of opioids for pain management which inhibit cellular and humoral immunity, and might even promote angiogenesis and tumor growth[10-12].

Regional anesthesia and analgesia techniques attenuate perioperative tumor-promoting effects by blocking afferent signaling to the central nervous system. Thus, regional techniques might reduce the neuroendocrine response to surgery more effectively than general anesthesia. Furthermore, regional analgesia decreases the need for volatile anesthetics and opioids. Regional analgesia might thus help maintain perioperative anti-cancer immune function, notably natural killer cell activity, and thus reduce the risk of circulating tumor cells developing into clinical metastases[13-16].

Potential benefit of regional analgesia for cancer recurrence is supported by animal investigations. For example, a study in rats compared halothane alone combined with either systemic morphine or with spinal block using bupivacaine with morphine. General anesthesia alone increased tumor retention in the lungs by up to 17-fold. Additionally, natural killer cell activity was depressed by general anesthesia[7]. Another study compared general anesthesia with sevoflurane alone versus spinal blocks combining bupivacaine and morphine. Addition of the spinal block to general anesthesia attenuated suppression of tumoricidal liver mononuclear cells and consequently reduced promotion of tumor metastasis[17]. Animal evidence is thus largely consistent in suggesting benefit from regional analgesia and from reducing volatile anesthesia and opioid use.

Subsequent retrospective analyses in humans were encouraging. One compared combined general anesthesia with paravertebral analgesia versus general with morphine analgesia for breast cancer and reported that paravertebral analgesia reduced cancer recurrence[18]. Another retrospective analysis reported that epidural analgesia reduced biochemical recurrence of prostate cancer by 57%[19]. However, many other retrospective analyses found no association between regional anesthesia and cancer outcomes[20-23], leaving the overall record mixed.

Because purpose-designed trials of cancer recurrence naturally take a long time, investigators initially re-purposed previous randomized trials that were conducted for other purposes. For example, a team re-evaluated patients who participated in the MASTER trial.[24] They identified 503 patients who had surgery for cancer and were able to obtain long-term follow-up information in 446 of them. Two other re-analyses evaluated 99 patients who had prostatectomies for prostate cancer comparing general to general plus epidural analgesia and 132 patients who had intra-abdominal surgery via midline or bilateral subcostal incisions for non-benign cancer resection comparing general anesthesia with epidural blocks versus with fentanyl analgesia followed by continuous subcutaneous morphine. None of these trials demonstrated notable differences in cancer-associated outcomes[25,26]. The only exception was a re-analysis that compared survival in patients randomized to general anesthesia with and without epidural supplementation for colon cancer surgery. A post hoc subgroup analysis implausibly found enhanced survival in the epidural group only in patients without metastasis before 1.5 years[27]. Analyses of trials conducted for other purposes thus provide little support for a benefit of regional analgesia for reducing cancer recurrence.

There have been three major trials of regional analgesia on cancer recurrence. The first randomized 2,132 patients having potentially curative primary breast cancer surgery to paravertebral analgesia or conventional opioid analgesia. Cancer recurrence was similar in each group after a median follow-up time of 36 months (hazard ratio 0.97, 95% CI 0.74–1.28; p=0.84). The authors noted that breast surgery causes less operative stress and pain than major

abdominal and thoracic surgery, and postulated that regional analgesia might yet be beneficial for such cases.[28]

The next trial therefore compared overall survival and cancer-free survival in patients randomized to combined general-epidural anesthesia versus general anesthesia alone for major abdominal cancer resections. In a total of 1,712 patients with a median follow-up duration of 66 months, there were no differences in terms of mortality (adjusted hazard ratio, 1.07; 95% CI, 0.92 to 1.24; P = 0.408) or recurrence-free survival (adjusted hazard ratio, 0.97; 95% CI, 0.84 to 1.12; P = 0.692)[29].

The third major trial randomized 400 patients having video-assisted thoracoscopic lung cancer resection to general anesthesia alone or general anesthesia combined with thoracic epidural analgesia. At a median follow-up duration of 32 months, epidural analgesia did not reduce recurrence-free (adjusted hazard ratio, 0.90; 95% CI, 0.60 to 1.35; P = 0.608), overall (adjusted hazard ratio, 1.12; 95% CI, 0.64 to 1.96; P = 0.697), or cancer-specific survival (adjusted hazard ratio, 1.08; 95% CI, 0.61 to 1.91; P = 0.802).[30] Thus, even when restricting analysis to patients experiencing high surgical stress and considerable postoperative pain, regional techniques failed to reduce cancer recurrence.

While regional anesthetic techniques have many benefits, three robust trials which randomized a total of 4,244 patients conclusively demonstrate that regional analgesia does not reduce recurrence of breast, abdominal, and lung cancer (Figure). Given the quality and diversity of evidence, further investigations into regional analgesia are unlikely to prove fertile. Case closed. Instead, perioperative investigators might better focus on comparisons between volatile and intravenous anesthesia[31-33], and on adjuncts such as COX-2 inhibitors[34,35] and lidocaine[36].

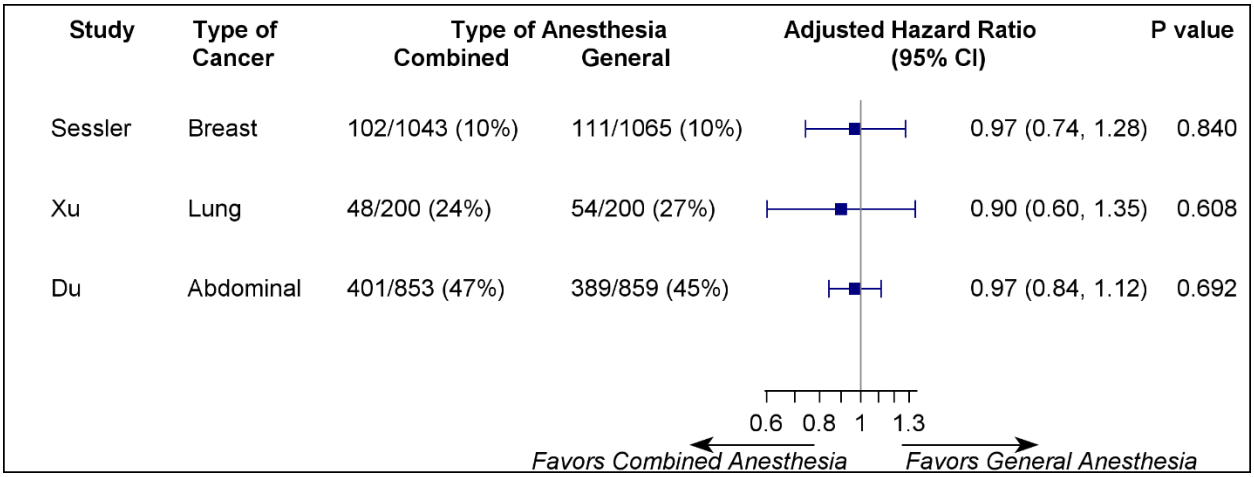

Figure legend: Forest plot of hazard ratios for cancer recurrence and recurrence-free survival from three major trials of regional analgesia in patients having cancer surgery. There was no evidence of benefit in any of the trials.

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