Clin Orthop Relat Res (2014) 472:1434–1441
DOI 10.1007/s11999-013-3306-y

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

SYMPOSIUM: PERIOPERATIVE PAIN MANAGEMENT IN ORTHOPAEDIC SURGERY

Can Regional Anesthesia and Analgesia Prolong Cancer Survival After Orthopaedic Oncologic Surgery?

Juan P. Cata MD, Mike Hernandez MS, Valerae O. Lewis MD, Andrea Kurz MD

Published online: 1 October 2013

Abstract

Background The perioperative period of major oncologic surgery is characterized by immunosuppression, angiogenesis, and an increased load of circulating malignant cells. It is a window period in which cancer cells may seed, invade, and proliferate. Thus, it has been hypothesized that the use of regional anesthesia with the goal of reducing surgical stress and opioid and volatile anesthetic consumption would avoid perioperative immune suppression and angiogenesis and ultimately cancer recurrence.

Questions/purposes We performed a systematic review of the literature on the use of regional anesthesia and postoperative analgesia to improve cancer-related survival after oncologic surgery. Our primary topic of interest is survival after orthopaedic oncologic surgery, but because that literature is limited, we also have systematically reviewed the question of survival after breast, gastrointestinal, and genitourologic cancers.

Methods We searched the PubMed and Embase databases with the search terms: "anesthesia and analgesia", "local neoplasm recurrence", "cancer recurrence", "loco-regional neoplasm recurrence", "disease-free survival", and "cumulative survival rates". Our initial search of the two databases provided 836 studies of which 693 were rejected. Of the remaining 143 studies, only 13 articles qualified for inclusion in this systematic review, based on defined inclusion criteria. All these studies had retrospective design. Due to the high heterogeneity among the identified studies and the complete absence of randomized controlled trials from the literature on this topic, the results of a meta-analysis would be heavily confounded; hence, we instead performed a systematic review of the literature.

Results No eligible studies addressed the question of whether regional anesthesia and analgesia have an impact on survival after musculoskeletal cancer surgery. Only one relevant clinical study was identified on regional breast cancer survival; it suggested a benefit. The literature on gastrointestinal and genitourinary surgery was larger but

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research* editors and board members are on file with the publication and can be viewed on request.
This work was performed at The University of Texas–MD Anderson Cancer Center, Houston, TX, USA.

J. P. Cata (✉)
Department of Anesthesiology and Perioperative Medicine, The University of Texas–MD Anderson Cancer Center, 1515 Holcombe Blvd, Box FC13, Houston, TX 77030, USA
e-mail: jcata@mdanderson.org

J. P. Cata
Outcomes Research Consortium, Cleveland, OH, USA

M. Hernandez
Department of Biostatistics, The University of Texas–MD Anderson Cancer Center, Houston, TX, USA

V. O. Lewis
Department of Orthopedic Oncology, The University of Texas–MD Anderson Cancer Center, Houston, TX, USA

A. Kurz
Department of Outcomes Research and General Anesthesia, Cleveland Clinic, Cleveland, OH, USA

mixed, although some preliminary studies do suggest a benefit of regional anesthesia on survival after oncologic surgery in those patient populations.

Conclusions Although basic science studies suggest a potential benefit of regional anesthesia and stress response reduction in cancer formation, we found little clinical evidence to support the theory that regional anesthesia and analgesia improve overall patient survival after oncologic surgery.

Introduction

Forty years ago, the overall prognosis for patients with malignant musculoskeletal tumors was dismal. Fortunately, overall survival has improved, a result of improvements in surgical techniques and perioperative care [1, 14]. However, despite better survival, many patients still develop local recurrence or distant metastasis after primary tumor resection [14]. Recurrences are related to the biology of the tumor, poor tumor responsiveness to chemotherapy and/or radiation, micrometastasis, and circulating malignant cells present in the blood stream before, during, and after surgery [1, 36].

Preclinical evidence suggests that tumor growth is facilitated by surgical stress, volatile anesthetics, opioids, and blood transfusions [4]. For instance, surgical stress induces the release of catecholamines that act on adrenergic receptors located in the membrane of cancer cells, thus stimulating their proliferation and invasiveness [33, 34]. Opioids are the most commonly used analgesics in the perioperative period. Opioids activate the μ receptors located on the surface of non-small-cell lung and breast cancer cells, triggering their proliferation and invasion [24]. In contrast, morphine induces apoptosis in other cancer cell lines such as lung and breast carcinoma [18, 19]. In healthy humans and in those with cancer, the administration of fentanyl or morphine is associated with increased plasma concentrations of IL-10, suggesting a predominant antiinflammatory and immune suppressive profile [10, 21, 38].

The perioperative period is characterized by intense inflammation manifested by increased circulating concentrations of proinflammatory cytokines such as IL-1β and IL-6 [29]. These two cytokines stimulate the activity of the cyclooxygenase-2 (COX-2) enzyme [20]. Increased activity of the COX-2 enzyme has been linked to cancer formation. In the perioperative period, the administration of the COX inhibitor etodolac to animals having surgery diminished the number of metastases, suggesting that the perioperative administration of COX inhibitors may reduce tumor burden after oncologic surgery [16]. In summary, the overall effect of the perioperative period on cancer biology is tumorigenic and immunosuppressive.

A number of clinical studies in various surgical disciplines have sought to determine whether regional anesthesia and analgesia improve survival after oncologic surgery, and Chen and Miao [5] recently conducted a meta-analysis of such studies. However, that study included all human cancers in its analysis, likely introducing considerable bias in the interpretation of the results since recurrence rates of different cancers vary, confounding the effect of the regional anesthesia on recurrence. Moreover, the dataset in that study demonstrated significant heterogeneity, and the authors did not discriminate between intraoperative and postoperative regional analgesia. For these reasons, we believed it was important to perform a systematic review of the literature on the use of regional anesthesia and postoperative analgesia to improve cancer-related survival after oncologic surgery. Our primary topic of interest is survival after orthopaedic oncologic surgery, but because that literature is limited, we also have systematically reviewed the question of survival after breast, gastrointestinal, and genitourologic cancers.

Search Strategy and Criteria

We searched the PubMed and Embase databases in the first week of March 2013. We queried the PubMed database for studies published between January 1, 1945, and March 7, 2013, and searched the Embase database for publications between January 1, 1980, and March 7, 2013. The following search terms were used: "anesthesia and analgesia", "local neoplasm recurrence", "cancer recurrence", "loco-regional neoplasm recurrence", "disease-free survival", and "cumulative survival rates". We electronically searched all manuscripts and limited our findings to manuscripts published only in English. We did not include any conference proceedings in our search.

Abstracts of possible qualifying studies were retrieved and examined for relevance. Two independent authors (JPC, MH) reviewed the selected manuscripts, and after careful discussion of each manuscript, a final decision was made based on the adherence to a priori determined inclusion and exclusion criteria. The inclusion criteria included (1) patients with cancer, (2) adults, (3) primary or metastatic tumor resection, (4) general anesthesia and/or regional anesthesia or analgesia used in the perioperative period, and (5) randomized controlled trials (RCTs), prospective trials, and cohort studies comparing the above-mentioned anesthesia and analgesia techniques. Case series, case reports, experimental translational or basic science studies, and narrative reviews were excluded for the analysis but still considered as proof of knowledge or concept.

Since our search identified no RCTs, we assessed the quality of the included observational studies by using the

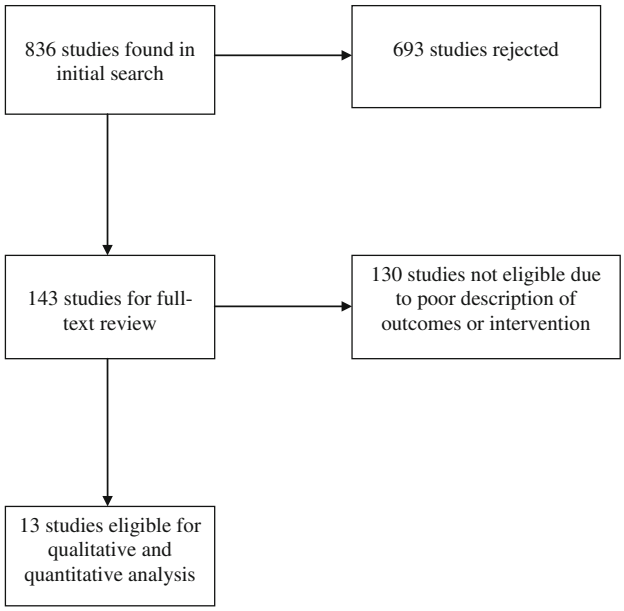

Fig. 1 A flow diagram illustrates the process of article selection for analysis.

STROBE checklist [35]. All the publications that met the inclusion criteria were graded based on the determinants for quality of evidence published by the Oxford Centre for Evidence-based Medicine Level of Evidence: Level 1: systematic review of RCTs; Level 2: RCTs; Level 3: nonrandomized controlled cohort studies; Level 4: case series or case-control or historically controlled studies; and Level 5: expert opinion [32].

The initial search of the two databases provided 836 studies of which 693 were rejected (Fig. 1). From the 143 papers considered for full revision, we excluded 130 because there was no mention of anesthesia-analgesia techniques or clinically relevant outcomes. Hence, only 13 articles were included in the systematic review [2, 3, 6–8, 11, 13, 15, 17, 23, 25, 28, 37]. All these studies had retrospective design (Level 2b according to the Oxford Centre for Evidence-based Medicine Level of Evidence) and were published between 2006 and 2013. We identified six reviews, one meta-analysis, and one study that compared neuraxial anesthesia and general anesthesia for brachytherapy placement. The identified meta-analysis [5] was not included in the analysis; however, we hand-searched its references and confirmed that no new studies have been published since its publication.

Of the selected papers, there were important differences in sample sizes, statistical analysis (multivariate Cox proportional analysis with or without propensity score matching), cancer histology, timing of the initiation of the regional analgesia (intraoperative versus postoperative), and type of local anesthetic or opioid used and even no report of the type of local anesthetic solutions used. Perhaps more importantly, the outcome being evaluated was defined differently in each study. These differences, compounded by the retrospective and observational design of the articles, may be responsible for the controversial results. Considering the high heterogeneity among the identified studies, we did not conduct a meta-analysis due to the difficulty in coalescing consistent end points across relevant studies and the inability to generate summary statistics. Hence, we conducted a systematic review of the literature instead. The studies were summarized in an evidence table providing the informative details of each study (Table 1). We describe study findings according to the origin of the cancers.

Results

Regional Analgesia/Anesthesia and Musculoskeletal Cancer Recurrence

In this systematic review, we identified no qualifying studies that assessed the impact of regional anesthesia and analgesia on cancer recurrence after musculoskeletal oncologic surgery. Due to the variety of cancers within this group of tumors and their aggressive nature, it is difficult to speculate whether the use of any intraoperative and postoperative regional analgesia techniques would have a significant impact on recurrence-free survival or overall survival.

Regional Analgesia and Breast Cancer Recurrence

Only one study investigated the effect of regional analgesia on breast cancer recurrence [13]. The authors studied 129 patients and demonstrated that the use of paravertebral block in patients who had a mastectomy with axillary clearance was associated with better recurrence-free survival rate than that in patients treated with intravenous (morphine) patient-controlled analgesia (IVPCA) (6% and 24 %, respectively, $p = 0.013$). All patients received general anesthesia, and as expected, those treated with additional paravertebral block had lower postoperative pain scores and opioid consumption. The lower recurrence rates observed in the regional analgesia group was perhaps due to a lower number of local and axillary recurrences. This suggests either a regional benefit of the paravertebral block or a higher rate of surgical failures in the IVPCA group, although all patients underwent surgery by the same surgeon. This study has several limitations, including the relatively small sample size and its retrospective and observational design, and perhaps due to lack of propensity

Table 1. Summary of characteristics of the studies included in our analysis

Study	Year	Cancer	Intervention	Outcome	Hazard ratio (95% CI)	Comments	Quality assessment (STROBE checklist)
Exadaktylos et al. [13]	2006	Breast	Paravertebral block analgesia vs IV analgesia	RFS	0.21 (0.06–0.71) (p = 0.012)	Paravertebral analgesia associated with longer BFS	Incomplete
Christopherson et al. [6]	2008	Colon	General anesthesia vs epidural general anesthesia	OS	Nonmetastasis: 4.65 (1.45–15.42) (p = 0.012) Metastasis: (p = 0.22)	Epidural use was associated with better OS in nonmetastasis patients early after treatment (1.42 years)	Incomplete
Cummings et al. [7]	2012	Colon	Epidural vs traditional analgesia	RFS	1.05 (0.95–1.15) (p = 0.28)	No association	Incomplete
				OS	0.45 (0.27–0.75) (p = 0.002)	Epidural technique associated with longer OS	
Day et al. [8]	2012	Colon	Epidural vs spinal vs IV analgesia	DFS	NR (p = 0.75)	No association	Incomplete
				OS	NR	No association	
Gupta et al. [17]	2011	Colon	Epidural vs IV analgesia	OS	0.82 (0.3–2.19) (p = 0.68)	No association	Incomplete
		Rectal	Epidural vs IV analgesia	OS	0.45 (0.22–0.90) (p = 0.025)	Epidural technique associated with longer OS	Incomplete
Myles et al. [28]	2011	Colon	Epidural vs IV analgesia	RFS	0.91 (0.69–1.2) (p = NR)	No association	Incomplete
Lai et al. [23]	2012	HCC	Epidural vs general anesthesia	RFS	4.31 (2.24–8.29) (p < 0.001)	General anesthesia associated with longer RFS	Incomplete
Capmas et al. [3]	2012	Ovarian	Epidural anesthesia plus analgesia vs nonepidural analgesia	RFS	1.18 (0.61–2.31) (p = 0.56)	Epidural use was not associated with better RFS or OS	Incomplete
				OS	1.25 (0.39–4.04) (p = 0.71)		
de Oliveira et al. [11]	2011	Ovarian	Epidural vs IV analgesia	RFS	0.86 (0.52–1.41) (p = 0.54)	No association	Incomplete
			Epidural anesthesia plus analgesia vs IV analgesia	RFS	0.37 (0.19–0.73) (p = 0.004)	Epidural anesthesia plus analgesia associated with longer OS than IV analgesia	Incomplete
Lin et al. [25]	2011	Ovarian	Epidural anesthesia plus analgesia vs general anesthesia plus IV analgesia	OS	1.32 (1.08–1.69) (p = 0.039)	Epidural anesthesia plus analgesia associated with longer OS than IV analgesia	Incomplete
Myles et al. [28]	2011	Ovarian	Epidural vs IV analgesia	RFS	0.81 (0.42–1.57) (p = NR)	NR	Incomplete
Biki et al. [2]	2008	Prostate	Epidural vs IV analgesia	BFS	0.48 (0.23–1.00) (p = 0.049)	Epidural technique associated with longer BFS	Incomplete
Wuethrich et al. [37]	2010	Prostate	Epidural vs IV analgesia	BFS	1.14 (0.84–1.54) (p = 0.399)	No association	Incomplete
				CPFS	0.45 (0.27–0.75) (p = 0.002)	Epidural technique associated with longer CPFS	
				CSS	0.45 (0.18–1.13) (p = 0.089)	No association	
				OS	0.61 (0.29–1.28) (p = 0.19)	No association	
Forget et al. [15]	2011	Prostate	Epidural vs IV analgesia	BFS	0.84 (0.52–1.17) (p = 0.31)	No association	Incomplete
Myles et al. [28]	2011	Bladder Prostate	Epidural vs IV analgesia	RFS	1.67 (0.21–13.4) (p = NR)	NR	Incomplete

HCC = hepatocellular carcinoma; IV = intravenous; RFS = recurrence-free survival; OS = overall survival; DFS = disease-free survival; BFS = biochemical recurrence-free survival; CPFS = clinical progression-free survival; CSS = cause-specific survival; NR = not reported.

score matching analysis, it probably greatly overestimates effect size.

The same group of authors conducted a series of elegant clinical and experimental investigations to understand the findings of their original retrospective study. They demonstrated in vitro that morphine, independent of μ receptor activation, induced proliferation and invasion in two different cells lines of breast cancer [12]. In another series of clinical studies, the authors randomized patients with breast cancer undergoing mastectomy to general anesthesia with sevoflurane-opioid versus propofol-paravertebral block. They found that the serum of those patients who received propofol-paravertebral block inhibited in vitro breast cancer cell proliferation but not migration and had better control of stress response markers, metalloproteinases, and transforming growth factor β but higher levels of vascular endothelial growth factor C [9, 10, 26, 31].

In summary, the use of paravertebral analgesia was associated with a predominantly antitumor environment; whether this finding correlates with prolonged survival rates is still unknown. There are two large RCTs currently underway to answer this question (NCT01179308 and NCT00418457).

Postoperative Neuraxial Analgesia and Gastrointestinal Cancer Recurrence

The literature on gastrointestinal tumors is larger, but the results on the question of whether regional anesthesia techniques are associated with increased survival are inconclusive, perhaps owing to the diversity of tumor types in the published studies. Six studies on gastrointestinal cancers examined the impact of regional anesthesia on cancer recurrence and/or overall survival. Four of them studied colorectal cancer, one a variety of cancers but predominantly colorectal cancer, and one hepatocellular carcinoma [6–8, 23, 28]. While the conclusions were similar, there are important differences between the studies. First, the study by Cummings et al. [7] was a large population-based retrospective study of 40,377 patients without a clear description of the postoperative type of analgesia technique in the nonepidural group. In contrast, Day et al. [8] included 457 patients originally enrolled in RCTs, and this led to a more uniform postoperative intravenous analgesia technique. Also, Day et al. [8] distinguished between patients receiving epidural or spinal analgesia. The findings of these two studies are in agreement with a post hoc analysis of the Multicentre Australian Study of Epidural Anesthesia (the MASTER Anesthesia Trial). The MASTER Anesthesia Trial was a prospective RCT in which patients were allocated to abdominal surgery under combined epidural-general anesthesia and postoperative epidural analgesia versus general balanced anesthesia and postoperative intravenous opioid analgesia [28]. In that particular study, no association was found between the use of epidural anesthesia and recurrence-free survival. In a recent study of 655 patients, Gupta et al. [17] demonstrated that patients with rectal cancer treated with epidural analgesia had a better overall survival, but those with colon cancer did not (Table 1). These results are similar to those of Christopherson et al. [6]. Unfortunately, neither of those studies could establish whether the cause of death was cancer-related or not. Hence, based on these findings, it is difficult to speculate whether epidural analgesia had a clinically meaningful impact on cancer recurrence in patients with rectal cancer [6, 16].

In marked contrast to the above-mentioned studies, a retrospective study by Lai et al. [23] of patients with hepatocellular carcinoma who underwent radiofrequency ablation under either epidural or general anesthesia demonstrated an association between the use of epidural anesthesia and decreased recurrence-free survival (hazard ratio: 4.31; 95% CI: 2.24–8.29; $p < 0.001$). However, there was no association between regional anesthesia and overall survival (hazard ratio: 1.26; 95% CI: 0.81–1.97; $p = 0.312$). Interestingly, in the multivariate Cox analysis, the intraoperative and postoperative use of opioids was not associated with worse outcomes. The authors speculated that radiofrequency ablations may be more effective under general anesthesia because the referred pain usually observed during epidural anesthesia was better controlled under general anesthesia. Thus, longer or more frequent radiofrequency treatments could be given.

In summary, there is no clear evidence that the use of regional analgesia is associated with improved recurrence-free survival or overall survival in patients with gastrointestinal cancer.

Postoperative Neuraxial Analgesia and Genitourologic and Gynecologic Cancer Recurrence

Six retrospective studies have addressed the question of whether regional analgesia, specifically neuraxial analgesia, has a significant impact on recurrence after genitourologic cancers [2, 3, 11, 15, 25, 37] (Table 1). The results of three studies conducted in patients with prostate cancer are inconsistent [2, 15, 37]. The use of postoperative epidural analgesia improved biochemical parameters associated with cancer recurrence (rise in prostate-specific antigen after surgery) in the study by Biki et al. [2], who included 225 patients, but not in the study by Wuethrich et al. [37]. Interestingly, Wuethrich et al. [37] identified an improvement in clinical progression survival (defined as the time from surgery to clinical progression or death) but

not in cancer-specific and overall survival. Forget et al. [15] conducted the largest study that included 1111 patients and found that the use of regional analgesia was not associated with better biochemical recurrence-free survival. It is difficult to explain why these studies differed so dramatically in their main outcome. However, potential reasons include the possibility of confounding, differences in the definitions of the biochemical recurrence-free survival (defined as a postoperative rise in prostate-specific antigen > 0.2 ng/mL), and different anesthesia techniques.

The results of the three retrospective studies in patients with ovarian cancer likewise differed importantly from one another [3, 11, 25]. Briefly, de Oliveira et al. [11] demonstrated that only the use of combined intraoperative epidural-general analgesia followed by postoperative epidural analgesia (n = 26) was associated with better recurrence-free survival compared to either general anesthesia/intravenous analgesia (n = 127) or general anesthesia/postoperative epidural analgesia (n = 29). This is in agreement with Lin et al. [25] who showed in 143 patients that surgery under epidural anesthesia/analgesia was more beneficial to patient survival than surgery under general anesthesia and postoperative intravenous opioid analgesia. The findings of these two studies highlight the importance of the intraoperative use of epidural anesthesia, which was associated at least in the work of de Oliveira et al. [11] with less perioperative use of opioids. However, Capmas et al. [3] showed that the use of epidural analgesia was not associated with better survival. These studies suggest that intraoperative opioids and surgical stress may be linked with minimal residual cancer growth either by acting directly on cancer cells or indirectly by causing immunosuppression, although this last statement is merely speculative.

In summary, the literature is mixed on a potential benefit of regional anesthesia on cancer survival outcomes after ovarian and prostate cancer surgery.

Discussion

Local anesthetics are the main drugs used in regional anesthesia and analgesia for postoperative pain management of patients with orthopaedic oncologic diseases. These drugs have effects on cancer cells. For instance, lidocaine decreases the ability of fibrosarcoma and osteosarcoma cells to invade and form metastases [27]. Opioids are the most commonly used analgesic in the perioperative period. Researchers have investigated the effects of morphine in osteosarcoma cells; interestingly, morphine does not appear to enhance the in vivo growth of those cells [22]. Increased activity of the COX-2 enzyme has been linked to cancer formation. Osteosarcoma and Ewing's sarcoma cells express high levels of the enzyme and the administration of COX-2 inhibitors appears to decrease tumor growth and invasion [30]. In summary, the preclinical evidence suggests that current analgesic and anesthetic approaches may influence the proliferation and invasiveness characteristics of musculoskeletal cancer cells. Whether these basic science findings will translate into clinically beneficial treatments is far from clear; this question was the main topic of this systematic review.

This systematic review had a number of limitations, and our findings should be interpreted in light of these. The literature on nonmusculoskeletal tumors was mixed and limited due to the retrospective nature of the studies. Although we found no studies that addressed cancer-related survival in patients undergoing orthopaedic tumor surgery, we will not know whether regional anesthesia has a significant impact on cancer recurrence until an RCT is conducted in this population of patients. Phase III RCTs should be done to test the efficacy of perioperative interventions on cancer-related survival outcomes; however, several challenges are present in the design, development, and conduction of such clinical trials. For instance, the conduction of such trials will be difficult in musculoskeletal tumors due to the low incidence in the population, which will limit the accrual of patients into the study. Lack of funding and poor cooperative effort among perioperative physicians will also be major challenges to performing RCTs.

Surgery remains one of the main therapies for many types of solid organ tumors including musculoskeletal cancers. Unfortunately, several clinical interventions, including surgery and general anesthetics and analgesics, may either increase immunosuppression or stimulate cancer growth [4]. The use of regional anesthesia and analgesia to avoid volatile anesthetics and opioid-related immunosuppression and to ameliorate surgical stress may therefore be an attractive option in the hopes of decreasing the likelihood of cancer recurrence. A recent meta-analysis [5] indicated that the use of regional anesthesia and analgesia was not associated with better recurrence-free survival but was associated with improved overall survival. However, as discussed in the Introduction, there were several problems associated with that report, which prompted us to conduct our systematic review. While we are able to present preclinical instead of clinical data in this systematic review about patients who were treated for nonmusculoskeletal tumors, we found no clinical studies addressing whether regional anesthesia may improve cancer-related survival in patients undergoing musculoskeletal oncologic surgery.

In conclusion, while a number of good basic science papers have proposed plausible reasons why regional anesthesia may reduce cancer recurrences, the clinical literature is small, heterogeneous, and mixed in terms of its results.

The question has not yet been investigated in musculoskeletal tumor surgery. We believe it ought to be. Multicenter RCTs are needed to test the hypothesis that regional anesthesia and analgesia might improve recurrence-free survival and overall survival after oncologic surgery.

References

1. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, Kotz R, Salzer-Kuntschik M, Werner M, Winkelmann W, Zoubek A, Jürgens H, Winkler K. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clinical Oncol.* 2002;20:776–790.
2. 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.
3. Capmas P, Billard V, Gouy S, Lhommé C, Pautier P, Morice P, Uzan C. Impact of epidural analgesia on survival in patients undergoing complete cytoreductive surgery for ovarian cancer. *Anticancer Res.* 2012;32:1537–1542.
4. Cata JP, Gottumukkala V, Sessler DI. How regional analgesia might reduce postoperative cancer recurrence. *Eur J Pain Suppl.* 2011;5:345–355.
5. 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.
6. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: a variation associated with choice of anesthesia. *Anesth Analg.* 2008;107:325–332.
7. Cummings KC 3rd, Xu F, Cummings LC, Cooper GS. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: a population-based study. *Anesthesiology.* 2012;116:797–806.
8. 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.
9. Deegan CA, Murray D, Doran P, Ecimovic P, Moriarty DC, Buggy DJ. Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro. *Br J Anaesth.* 2009;103:685–690.
10. Deegan CA, Murray D, Doran P, Moriarty DC, Sessler DI, Mascha E, Kavanagh BP, Buggy DJ. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Reg Anesth Pain Med.* 2010;35:490–495.
11. de Oliveira GS Jr, Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med.* 2011;36:271–277.
12. Ecimovic P, Murray D, Doran P, McDonald J, Lambert DG, Buggy DJ. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. *Br J Anaesth.* 2011;107:916–923.
13. 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.
14. Federman N, Bernthal N, Eilber FC, Tap WD. The multidisciplinary management of osteosarcoma. *Curr Treat Options Oncol.* 2009;10:82–93.
15. Forget P, Tombal B, Scholtes JL, Nzimbala J, Meulders C, Legrand C, Van Cangh P, Cosyns JP, De Kock M. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? *Eur J Anaesth.* 2011;28:830–835.
16. Goldfarb Y, Sorski L, Benish M, Levi B, Melamed R, Ben-Eliyahu S. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. *Ann Surg.* 2011;253:798–810.
17. Gupta A, Bjornsson A, Fredriksson M, Hallböök O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: a retrospective analysis of data from 655 patients in central Sweden. *Br J Anaesth.* 2011;107:164–170.
18. Hatsukari I, Hitosugi N, Matsumoto I, Nagasaka H, Sakagami H. Induction of early apoptosis marker by morphine in human lung and breast carcinoma cell lines. *Anticancer Res.* 2003;23:2413–2417.
19. Hatsukari I, Hitosugi N, Ohno R, Hashimoto K, Nakamura S, Satoh K, Nagasaka H, Matsumoto I, Sakagami H. Induction of apoptosis by morphine in human tumor cell lines in vitro. *Anticancer Res.* 2007;27:857–864.
20. Honda K. Interleukin-6 and soluble interleukin-6 receptor suppress osteoclastic differentiation by inducing PGE(2) production in chondrocytes. *J Oral Sci.* 2011;53:87–96.
21. Kim MH, Hahm TS. Plasma levels of interleukin-6 and interleukin-10 are affected by ketorolac as an adjunct to patient-controlled morphine after abdominal hysterectomy. *Clin J Pain.* 2001;17:72–77.
22. King T, Vardanyan A, Majuta L, Melemedjian O, Nagle R, Cress AE, Vanderah TW, Lai J, Porreca F. Morphine treatment accelerates sarcoma-induced bone pain, bone loss, and spontaneous fracture in a murine model of bone cancer. *Pain.* 2007;132:154–168.
23. Lai R, Peng Z, Chen D, Wang X, Xing W, Zeng W, Chen M. The effects of anesthetic technique on cancer recurrence in percutaneous radiofrequency ablation of small hepatocellular carcinoma. *Anesth Analg.* 2012;114:290–296.
24. Lennon FE, Mirzapoiazova T, Mambetsariev B, Salgia R, Moss J, Singleton PA. Overexpression of the mu-opioid receptor in human non-small cell lung cancer promotes Akt and mTOR activation, tumor growth, and metastasis. *Anesthesiology.* 2012;116:857–867.
25. 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.
26. 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.
27. Mammoto T, Higashiyama S, Mukai M, Mammoto A, Ayaki M, Mashimo T, Hayashi Y, Kishi Y, Nakamura H, Akedo H. Infiltration anesthetic lidocaine inhibits cancer cell invasion by modulating ectodomain shedding of heparin-binding epidermal growth factor-like growth factor (HB-EGF). *J Cell Physiol.* 2002;192:351–358.
28. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI; ANZCA Trials Group Investigators. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. *BMJ.* 2011;342:d1491.
29. Narita S, Tsuchiya N, Kumazawa T, Maita S, Numakura K, Obara T, Tsuruta H, Saito M, Inoue T, Horikawa Y, Satoh S, Habuchi T. Comparison of surgical stress in patients undergoing open versus laparoscopic radical prostatectomy by measuring perioperative serum cytokine levels. *J Laparoendosc Adv Surg Tech A.* 2013;23:33–37.
30. Naruse T, Nishida Y, Hosono K, Ishiguro N. Meloxicam inhibits osteosarcoma growth, invasiveness and metastasis by COX-2-

dependent and independent routes. *Carcinogenesis.* 2006;27: 584–592.
31. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC. Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. *Anesth Analg.* 2005;100:244–249.
32. Phillips BB, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. Oxford Centre for Evidence-based Medicine Levels of Evidence. 2011. Available at: http://www.pdptoolkit.co.uk/Files/ebm/cebm/Doing%20ebm/levels_of_evidence.htm. Accessed September 13, 2013.
33. Sloan EK, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangnukul V, Arevalo JM, Morizono K, Karanikolas BD, Wu L, Sood AK, Cole SW. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res.* 2010;70:7042–7052.
34. Sood AK, Bhatty R, Kamat AA, Landen CN, Han L, Thaker PH, Li Y, Gershenson DM, Lutgendorf S, Cole SW. Stress hormone-mediated invasion of ovarian cancer cells. *Clin Cancer Res.* 2006;12:369–375.
35. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370:1453–1457.
36. Wong IH, Chan AT, Johnson PJ. Quantitative analysis of circulating tumor cells in peripheral blood of osteosarcoma patients using osteoblast-specific messenger RNA markers: a pilot study. *Clin Cancer Res.* 2000;6:2183–2188.
37. Wuethrich PY, Hsu Schmitz SF, Kessler TM, Thalmann GN, Studer UE, Stueber F, Burkhard FC. Potential influence of the anesthetic technique used during open radical prostatectomy on prostate cancer-related outcome: a retrospective study. *Anesthesiology.* 2010;113:570–576.
38. Yardeni IZ, Beilin B, Mayburd E, Alcalay Y, Bessler H. Relationship between fentanyl dosage and immune function in the postoperative period. *J Opioid Manag.* 2008;4:27–33.