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The Relationship Between Regional Anesthesia and Cancer: A Metaanalysis

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Background: Some studies have suggested using epidural analgesia after cancer surgery to reduce metastasis. This article examines the relationship between regional anesthesia (RA) and cancer metastasis in an array of cancers.

Methods: We conducted a review of the literature using PubMed and included 67,577 patients across 28 studies in a metaanalysis, evaluating the hazard ratios (HRs) of overall survival, recurrence-free survival, and biochemical recurrence-free survival.

Results: We found no benefit to RA as it relates to cancer. The HR was 0.92 for overall survival, 1.06 for recurrence-free survival, and 1.05 for biochemical recurrence-free survival. Despite the overall analysis showing no benefit, we found some benefit when we evaluated only the randomized trials. However, we found no significant benefit of RA when we evaluated the cancers (gastrointestinal, prostate, breast, and ovarian) individually.

Conclusion: This metaanalysis shows that RA has no overall survival, recurrence-free survival, or biochemical recurrence-free survival benefit. However, some individual studies have shown significant benefit in terms of cancer recurrence. Further, RA reduces the use of opioids, which has led to some secondary benefits. Further studies are needed to establish the benefits of RA as it relates to cancer.

Keywords: *Analgesics–opioid, angiogenesis inducing agents, morphine, neoplasm metastasis*

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INTRODUCTION

Cancer-related pain is a severe and debilitating problem affecting millions of patients. This pain can often be unbearable, and healthcare providers are often compelled to increase such patients' doses of opioid analgesia. However, research in animal models has shown that opioids are immunosuppressive[1-3] through mediating inflammation and modulating angiogenesis,[4-8] and the stresses associated with surgical procedures can also impair immunity. Therefore, alternative multimodal pain management techniques are required to reduce the negative impact of opioids and to attempt to minimize surgical stress. Regional anesthesia (RA) is becoming a popular choice for pain management for many healthcare providers, and some evidence suggests that RA may play a role in inhibiting cancer progression. Various theories have been proposed to explain how RA may inhibit cancer progression: inhibition of neuroendocrine stress by the sympathetic block,[9] effects of local anesthetics on inflammation of cancer cell proliferation,[10-12] and reduction of opioid consumption and its immunosuppressive[3,13] and proangiogenic effects.[6]

Tumor Metastasis

Cancer occurs at sites of injury and inflammation. These inflammatory mediators play a key role in cancer formation and progression. Cancer forms in the settings of DNA damage and alteration in the cell environment. These initial changes have been termed initiation, and these changes often persist until another cell injury leads to promotion. Promotion can be caused by inflammation or other injury that causes an imbalance of the tumor's metastatic potential and antimetastatic potential.[14-16] Promotion leads to the recruitment of inflammatory cells, release of chemical mediators, damage to the surrounding tissue, and eventually failure of apoptosis, leading to rapid cellular proliferation.[17] Initially, tumors are only weakly antigenic, but they continue to mutate over time and become more antigenic.[17]

Several theories explain how cellular proliferation and growth occur, but one that is often cited is "seed and soil."[18] Tumor nutrition is initially met with diffusion, but with time, angiogenic factors are secreted, allowing neovascularization to occur. Neovascularization often occurs in response to injury and inflammation. An evolving tumor cannot progress beyond a 2-mm diameter size without angiogenesis occurring to meet its increasing metabolic requirements.[17] The mediators of this process include vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and prostaglandin E2 (PGE2).[18] VEGF stimulates signaling pathways that lead

to proliferation and migration of endothelial cells, increase vascular permeability, and—if tumor cells express tyrosine kinase VEGF receptors—lead to de-differentiation and tumor spread in an autocrine manner.[18,19] MMPs lead to degradation and remodeling of the extracellular matrix.[18,20] PGE2 is important in phagocyte-mediated immunity and in limiting the potential harmful activation of cytotoxic cells.[18] PGE2 has been shown to play an important role in cancer by inhibiting apoptosis, stimulating angiogenesis, enhancing invasion,[18] and enhancing migration and invasion via activation of the epidermal growth factor receptor (EGFR).[21] Of note, mutations of EGFR have been linked to several cancers.[21] In the postoperative period, PGE2, which is also produced by tissue injury and postoperative wound healing, may mediate metastatic progression.[22] The cytokines TNF-α and TGF-β are involved in systemic inflammation and function in the regulation of immune cells. When the inflammation cascade is activated, cancer cells spread by entering the lymphatic system and, finally, the general circulation.

Cyclooxygenase (COX) plays an important role in the formation of prostaglandins. Concentrations of COX-2 are upregulated in various cancers including breast, prostate, and gastrointestinal (GI) cancers.[23] One of the main products of COX-2 is PGE2. Nonsteroidal antiinflammatory drugs (NSAIDs) are inhibitors of COX-1 and COX-2. Thus, animal and human studies have shown the benefit of NSAIDs in the prevention of cancer.[24] Melamed et al found that administration of indomethacin reduced the increase in lung metastasis caused by surgery in rats inoculated with mammary adenocarcinoma.[24] Similar findings were reported by Farooqui et al in breast cancer: increasing the level of PGE2 promoted survival in animal models.[25] Farooqui et al also identified the benefit of improved pain control, which has also been shown to decrease the inflammatory response and the potential for metastasis.[25]

Surgery and the Proangiogenic Response

Surgery often removes the bulk of the tumor cells, but individual tumor cells are occasionally left at the margins of the cancer, often referred to as micrometastasis.[26] The immunosuppressive effects of anesthesia are additive to those of surgery.[17] Many cancer cells are dormant for long periods of time, and surgery provides the opportunity for growth. Surgical stress has an effect on MMPs, the proteolytic enzymes that facilitate the penetration of the extracellular matrix and the basement membrane during metastasis.[20] Surgery plays 4 key roles in promoting metastasis: (1) management and disruption of tumor-releasing tumor cells into circulation,[27] (2) decreased circulation of antiangiogenic factors (angiostatin and endostatin),[28,29] (3) increased local and systemic release of growth factors after surgery,[30,31] and (4) postoperative immunosuppression.[32] When the primary tumor is removed, the tumor milieu and homeostasis within the body seem to be altered.[17,26] As a result, the balance between inducers and inhibitors can be altered, leading to additional activation of circulating tumor cells and metastasis.[26,33-38] Endostatin given in vivo, using a spontaneous metastasis model, is associated with a reduction in distant metastasis.[39] Open rather than laparoscopic surgeries worsen the homeostatic milieu because of increased inflammatory reactions.[32,40] The effects of surgery on antiangiogenic factors (ie, VEGF) have been shown in in vivo models of breast cancer following mastectomy[6] and in animal models of ovarian cancer.[37] If the surgery is complicated by blood transfusions or hypothermia, recurrence may be higher.[17] Immunosuppressed patients are also increasingly susceptible to cancer recurrence compared to patients with an intact immune system.[41] Patients with sarcoma; melanoma; myeloma; or skin, bladder, or kidney tumors have higher recurrence rates of metastasis if they are on immunosuppressive therapies.[41]

Experimental and clinical studies have shown that surgery inhibits T-cell, B-cell, and natural killer (NK) cell function for several days after a surgical insult.[42] In addition, the production of cytokines that favor cell-mediated immunity—such as interleukin (IL)-2, IL-12, and interferon (IFN)-gamma—decreases, and the production of cytokines that interfere with cell-mediated immunity—such as IL-10—increases.[17] Peak immunosuppression is thought to occur on postoperative day 3 and to provide an opportunity for the micrometastasis to grow.[17] A decrease in NK cell numbers is associated with increased susceptibility to cancer or metastases after oncologic surgery.[17] Additionally, there is a linear correlation between NK activity and metastatic activity.[35,43]

Further, the type of analgesia used plays a key role in determining immunity.[35] General anesthesia (GA) is thought to suppress the immune system.[44] Anesthetics may inhibit cell-mediated immunity[45] or produce an alteration in the balance between the proinflammatory and antiinflammatory cytokines.[46] In particular, NK cytotoxicity has been shown to be suppressed by various anesthetics. All volatile anesthetics reduce NK cell activity.[47-50] Fentanyl seems to have a greater suppressive effect on NK cell activity compared to ketamine and clonidine.[35] Beilin et al evaluated a group of 40 patients undergoing major surgery who were randomized to either a high-dose fentanyl regimen that included midazolam and isoflurane as necessary or a low-dose fentanyl regimen with anesthetic maintenance using nitrous oxide or isoflurane.[13] In vitro NK activity was suppressed in all patients receiving fentanyl, but high-dose fentanyl therapy was associated with a slower rate of recovery of NK cell activity compared to low-dose fentanyl.[13]

Melamed et al compared the effects of propofol, halothane, ketamine, and thiopental on NK cell activity and metastatic spread of tumor cells in rats.[50] They found that all of these agents, except propofol, reduce NK cell activity.[50] Further, propofol also reduces inflammatory cytokines.[50] All anesthetics except propofol increased lung metastases and tumor retention.[50] Ketamine had the greatest effect on metastasis, increasing the frequency of metastasis almost 2.5-fold.[50] This increase was reduced with use of a β-receptor antagonist (nadolol), a prostaglandin synthesis inhibitor (indomethacin), or both.[50] Further, administration of a β-receptor agonist, prostaglandin, or both promoted metastasis of tumor cells.[50] Similar conclusions were found by Sloan et al.[51] In animal models, the stress-induced neuroendocrine activation from surgery had a negligible effect on the growth of the primary tumor but induced a 30-fold increase in metastasis to distant tissues.[51] In these animal studies, the effect was theorized to be via β-

adrenergic signaling and inhibited via the β-antagonist propranolol.[51]

While use of anesthetics and analgesics may suppress NK cell activity, acute pain may also suppress NK cell activity.[52,53] Of note, perioperative psychological stress and anxiety impact the neuroendocrine stress response, exerting a significant effect on the microenvironment of the tumor or the micrometastasis.[54,55]

Role of Regional Anesthesia

RA may reduce the stress associated with surgery, reduce pain, and lead to improved neuroendocrine function and cytokine-mediated stress response. The addition of intraoperative epidural analgesia reduces the levels of cortisol, β-endorphin, and epinephrine.[56] RA may inhibit neuroendocrine stress via sympathetic block.[9] Bar-Yosef et al demonstrated that RA leads to reduced metastatic burden in rats inoculated with metastatic cells (MADB106) post-laparotomy.[9] Their study compared anesthetized rats that underwent laparoscopic intervention to rats that did not under 3 different anesthetic regimens and found no significant difference in the number of lung metastases between the anesthetic regimens but did find a significant difference between the groups with or without surgical intervention.[9] Volatile anesthetics suppress the immune system and negatively impact cancer spread. They have been shown to increase concentrations of VEGF and MMPs, known stimulators of angiogenesis, and to increase cancer cell migration in vitro.[20] Further, volatile anesthetics have been shown to upregulate hypoxia-inducible factors. These factors are thought to be protective of ischemia-reperfusion injury, but they have been shown to be influential in angiogenesis and cell migration.[57] In the Bar-Yosef et al study, surgery with halothane increased the number of metastases 2-fold compared to the control group.[9] The addition of RA, in particular spinal anesthesia, reversed this effect.[9]

Cytotoxic T cells (CTCs) play an important role in the development of cancer. Patients with high CTC counts, in opposition to primary localized lung cancer, have been shown to have complete remission at 5 years, while patients with low CTC counts were less likely to survive.[58] Further, tumor infiltration by CTCs has been associated with a positive prognosis in colorectal cancer.[59] Ahlers et al showed that epidural analgesia in abdominal surgery was associated not only with a higher number of T-helper (Th) cells but also with a higher number of lymphocytes and preserved IFN-gamma concentrations.[60] Clinically, the higher number of Th cells led to decreased liver metastasis.[60] Le Cras et al showed that the ratio of Th1 to Th2 cells was higher in patients who had prostate surgery with spinal anesthesia vs GA.[61]

RA influences the expression of several cytokines perioperatively, including increasing IL-4 and decreasing IL-10.[62] IL-4 increases the expression of Th1. Ahlers et al reached a similar conclusion and found that the ratio of Th1 to Th2 cells was increased in patients who received epidural analgesia.[60] In contrast, administration of fentanyl or morphine is associated with increased plasma concentrations of IL-10, suggesting a predominant antiinflammatory and immunosuppressive profile.[63,64] IL-10 reduces expression of Th1 and the presence of NK cells.[65] This effect can be additive to the effect of surgery.[17] Gupta et al demonstrated that morphine, a VEGF activator, stimulates endothelial cell proliferation via a mitogen-activated protein kinase.[6] Further, morphine inhibits apoptosis and promotes cell-cycle progression in endothelial cells.[6] Similarly, Singleton et al found that opioids induce VEGF receptor activation, resulting in endothelial cell migration that is a step for angiogenesis.[66] VEGF receptor activation was inhibited by methylnaltrexone, a peripherally acting opioid antagonist.[66]

METHODS

In an attempt to identify the areas in which RA may have a proven benefit on cancer progression, we performed a metaanalysis. We reviewed the literature, searching PubMed for "regional anesthesia and cancer angiogenesis" and "regional anesthesia and cancer recurrence." After duplicates were removed, the search yielded 285 abstracts for initial review, 100 of which discussed RA association with angiogenesis or cancer recurrence in humans. We excluded reviews, metaanalyses, editorials, opinion pieces, and articles that exclusively discussed intraoperative analgesia, did not provide a comparison between GA and RA, were written in languages other than English, or were unavailable as complete articles. If our author team knew of pertinent literature that did not include specific details for inclusion in the review, the corresponding authors were contacted for additional information. We also reviewed the references from the included articles to ensure no article had been overlooked. The primary factor for inclusion in this meta-analysis was a comparison between RA and GA. Twenty-eight articles met this inclusion criterion. Figure 1 illustrates the literature search methodology. The primary outcomes were overall survival, recurrence-free survival, and biochemical recurrence-free survival compared via hazard ratios (HRs).

HR is a measure of how often a particular event happens in one group (treatment group) compared to how often it occurs in the control group. HR provides opportunities for articles to be evaluated in a uniform fashion. Weighted HRs were obtained by averaging the HRs from each of the individual articles. The ratios were weighted to highlight the effects of sample size in the analysis. Some of the observational studies were large and had the potential to skew the analysis significantly. An HR >1 denotes increased risk, an HR <1 denotes decreased risk, and an HR equal to 1 denotes no change in risk. Both observational studies and randomized controlled trials (RCTs) were evaluated. Results from both observational studies and RCTs were analyzed individually and together to provide a comprehensive analysis. Further, some of the studies provided both recurrence-free intervals and mortality rates that were analyzed individually because they evaluated different metrics.

RESULTS

A total of 28 studies that evaluate the role of RA in cancer angiogenesis (Table 1) met our inclusion criteria.[29,55,67-92] Most studies were retrospective or observational, but we identified 3 randomized controlled trials.[68,71,78] The number of patients placed into the analysis from all the studies was 67,577. The pooled weighted HR for overall survival was 0.92

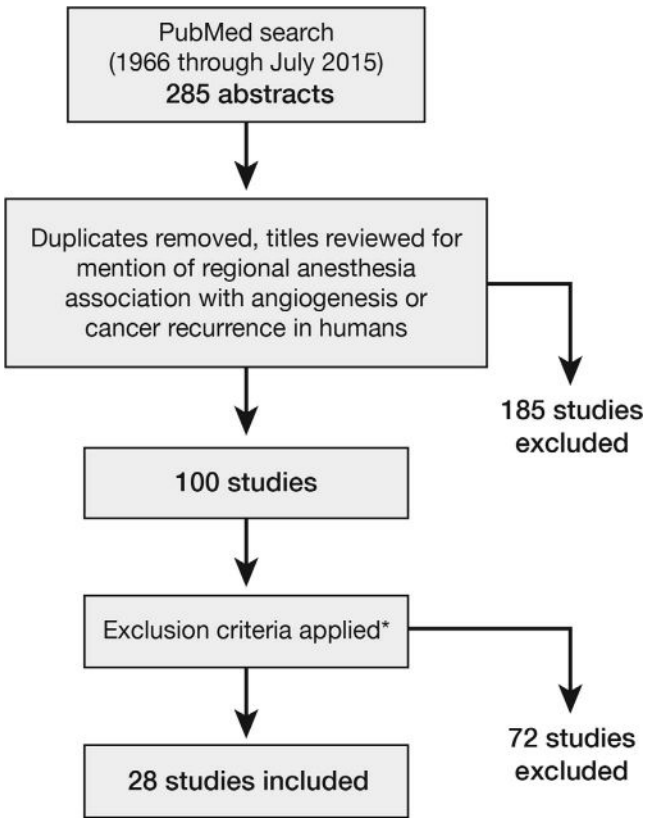

Figure 1. Literature search methodology. *Reviews, meta-analyses, editorials, opinion pieces, articles that exclusively discussed intraoperative analgesia, articles that did not compare general anesthesia and regional anesthesia, non–English language articles, and papers that were not available as complete articles were excluded.

(Figure 2), while the weighted recurrence-free survival was 1.06 (Figure 3), and the weighted HR for biochemical recurrence-free survival was 1.05 (Figure 4). Despite no significant overall survival benefit shown with the pooled averages, we found a slight survival benefit when evaluating just the RCTs, which had weighted HRs of 0.83 and 0.88 for overall survival and recurrence-free survival, respectively. On the aggregate, no survival benefit was seen in GI, prostate, breast, and ovarian cancers (Table 2). The HRs for overall survival and recurrence-free survival in GI cancers, especially colorectal, were 0.91[68,76,78,80,84] and 1.05,[55,78,80,82,83] respectively. However, excluding the large observational study (Cummings et al[80]), we found that use of RA had limited benefit in overall survival in GI cancers (HR=0.86). When this same study was excluded in the overall analysis, the HRs for overall survival and recurrence-free survival were 0.97[68,72,73,76-79,84-88] and 1.19,[55,67,70,74,78,82,83,86,87,92] respectively. Further, the HRs for overall survival and biochemical recurrence-free survival in prostate cancer were 1.06[72,73,87,88] and 1.05,[71,73,75,87,90] respectively, and the HR for overall survival in ovarian cancer was 0.94.[77,79,85]

DISCUSSION

For decades, opioids have been the analgesia of choice intraoperatively and postoperatively for patients with pain associated with cancer-related surgery. In addition to a potential mortality benefit, the benefits of reduced opioid usage include reducing the length of stay at hospitals and reducing side effects of opioid consumption such as respiratory depression or constipation.[93] Despite some trials showing favorability, when the cancers are evaluated macroscopically (overall survival, recurrence-free survival, and biochemical recurrence-free survival), no benefit is seen.[29,55,67-92]

Gastrointestinal Cancers

The results from evaluating the use of RA in colorectal cancers are mixed. Key factors in the benefits of RA include stage/type of colorectal cancer, age, timing of epidural, and American Society of Anesthesiology physical status classification (ASA class).[55,68,76,84] Gupta et al found that patients with rectal cancer had improved overall survival, but this benefit was not seen in patients with colon cancer.[76] Further, Christopherson et al conducted a small RCT that found improved overall survival in patients with epidurals up to 1.46 years after surgery if they had colorectal cancer without metastasis.[68] In the Surveillance, Epidemiology, and End Results (SEER) study, Cummings et al studied 49,655 patients who underwent surgery for colon cancer and found that those receiving epidural analgesia vs GA had no difference in recurrence-free survival but had a significant benefit in overall survival.[80] The RA group had an improved 5-year overall survival (61% vs 55%).[80] However, the authors found no difference in 4-year disease recurrence.[80] Holler et al found that patients with ASA class III-IV had a significant difference in 5-year overall survival associated with RA compared to GA.[84] However, this difference was not found in patients with ASA class I and II.[84]

Other studies have shown no benefit to RA. In an RCT of 446 patients, Myles et al found that the use of epidural block in abdominal surgery for colorectal cancer was not associated with improved cancer-free survival or 5-year mortality rate.[78] The small sample size of the study made it challenging to find subtle differences between the groups; however, larger differences could still be found. Gottschalk et al reported similar conclusions.[55] However, they found a lower risk of recurrence in the epidural group for patients aged >64 years.[55] In a group of 424 patients, Day et al found no difference in overall survival when comparing RA with GA.[81] Further, the length of stay was longer for patients in the epidural group at 5 days compared with 3 days for the spinal and patient-controlled analgesia group.[81]

In a retrospective study of 132 patients with a 17-year follow-up, Binczak et al found no statistical difference in recurrence-free survival between patients receiving bupivacaine thoracic epidural analgesia or fentanyl followed by continuous subcutaneous morphine.[83] However, the long follow-up may have minimized the impact of anesthesia technique.[83] While Heinrich et al did not find any direct benefits of RA for the management of esophageal cancer, they found that the reduced opioid use associated with RA led to fewer days in the intensive care unit and fewer days on mechanical ventilation, as well as reduced risk of reintubation, fewer days of antibiotics, and lower risk of perioperative anemia.[91] Despite these benefits, there was no difference in cancer recurrence, tumor spreading, or overall survival in a multivariate Cox analysis associated with epidural analgesia.[91]

Table 1. Summary of Available Human Trials Examining Cancer Recurrence and Regional Anesthesia

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Exadaktylos et al, 2006[67]	Retrospective cohort	Breast	GA vs combined GA/paravertebral anesthesia	50	79	Recurrence-free survival 0.21 (0.06-0.71); P=0.01	"Cancer surgery releases tumor cells into surrounding healthy tissue and into the systemic circulation. . . .Regional anesthesia and analgesia may help preserve immune function by attenuating the surgical stress response and diminishing the need for opioids."	Not controlled Study arms were different
Biki et al, 2008[29]	Retrospective cohort	Prostate	GA vs combined GA/EA	123	102	Biochemical recurrence 0.43 (0.22-0.83); P=0.049	"Open prostatectomy surgery with GA, substituting EA for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence."	
Christopherson et al, 2008[68]	Randomized controlled trial	Colorectal (nonmetastasized/ metastasized)	GA vs combined GA/EA	85	92	Overall survival (nonmetastatic) 0.22 (0.07-0.72); P=0.012 Overall survival (metastatic) 0.70 (0.40-1.24); P=0.22	"Epidural supplementation was associated with enhanced survival among patients without metastases before 1.46 years. EA had no effect on survival of patients with metastases."	Uncertain etiologies of death Short follow-up period Comorbidities of study groups
Gottschalk et al, 2010[55]	Retrospective cohort	Colorectal	GA vs combined GA/EA	256	253	Recurrence-free survival 0.82 (0.49-1.35); P=0.43	"Patients who received epidural therapy were more likely to be male, had a lower ASA score, a worse tumor grade, were more likely to have rectal cancer, received different surgical procedures, were less likely to have emergent surgery, received lower intraoperative FiO_2, received greater mean crystalloid volume, had a higher estimated blood loss but were less likely to be transfused, and were more likely to receive chemotherapy or radiation therapy."	Age of patients Short follow-up period
Ismail et al, 2010[70]	Retrospective cohort	Cervical (brachytherapy)	GA vs combined GA/EA	63	69	Recurrence-free survival 0.95 (0.54-1.67); P=0.863	"Using neuraxial anaesthesia during brachytherapy for patients with cervical cancer was not associated with a reduced risk of tumour recurrence and mortality when compared with general anaesthesia."	Lack of comorbidity data Small sample size

Table 1. Continued

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Tsui et al, 2010[71]	Randomized controlled trial	Prostate	GA vs combined GA/EA	49	50	Biochemical recurrence-free survival 1.33 (0.64-2.77); P=0.44	"No difference was observed between the epidural and [general] groups in disease-free survival at a median follow-up time of 4.5 years."	Varying definitions of biochemical recurrence Biochemical recurrence is not always indicative of early recurrence
Wuethrich et al, 2010[72]	Retrospective cohort	Prostate	GA vs combined GA/EA	103	158	Overall survival 0.61 (0.29-1.28); P=0.19 Progression-free survival 0.45 (0.27-0.75); P=0.002	"GA with EA was associated with a reduced risk of clinical cancer progression. However, no significant difference was found. . .in biochemical recurrence-free survival, cancer-specific survival, or overall survival."	Small study size
de Oliveira et al, 2011[74]	Retrospective cohort	Ovarian	Intraoperative EA vs postoperative EA vs postoperative non-EA	55	127	Recurrence-free survival 0.37 (0.19-0.73); P=NA	"The intraoperative use epidural group had a mean time to recurrence of 73 months, which was longer than either the epidural postoperative group. . .33 months or the no epidural group 38 months. . . .This may be a result of preservation of the immune system function."	Different stages of cancer in the study arms
Forget et al, 2011[75]	Retrospective cohort	Prostate	GA with different medications vs combined GA/EA	578	533	Biochemical recurrence-free survival 0.84 (0.52-1.17); P=0.31	"Intraoperative sufentanil administration is associated with an increased risk of cancer relapse after RRP, whereas EA, with local anaesthetic and opioid, was not associated with a significant effect."	Sufentanil use
Gupta et al, 2011[76]	Retrospective cohort	Colorectal (colon carcinoma)	GA vs combined GA/EA vs spinal anesthesia	562	93	Overall survival, colon cancer 0.82 (0.30-2.19); P=0.68 Overall survival, rectal cancer 0.45 (0.22-0.90); P=0.03	"No significant risk of death was found for colon cancer when comparing EA with patient-controlled analgesia, but a significantly increased risk of death was seen after rectal cancer when patient-controlled analgesia was used compared with EA."	Uncertain causes of death Different sized study arms

Table 1. Continued

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Lin et al, 2011[77]	Retrospective cohort	Ovarian	GA vs combined GA/EA	106	37	Overall survival 0.82 (0.70-0.96); $P=0.039$	"EA and analgesia for ovarian serous adenocarcinoma surgery may reduce mortality during the initial years of follow-up."	Different sized study arms Nonstandardized clinical care
Myles et al, 2011[78]	Randomized controlled trial	Colorectal	GA vs combined GA/EA	230	216	Overall survival 0.96 (0.79-1.17); $P=0.61$ Recurrence-free survival 0.95 (0.76-1.17); $P=0.61$	"Use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival."	Small study size
Capmas et al, 2012[79]	Retrospective cohort	Ovarian	GA vs combined GA/EA	47	47	Overall survival 1.25 (0.39-4.04); $P=0.71$ Risk-free survival 1.18 (0.61-2.31); $P=0.56$	"No statistical benefit was found for overall survival nor for recurrence-free survival following EA during cytoreductive surgery for ovarian carcinoma (in patients with complete cytoreduction)."	Small sample size
Cummings et al, 2012[80]	Retrospective cohort	Colorectal	GA vs combined GA/EA	9,278	40,377	Overall survival 0.91 (0.87-0.94); $P<0.001$ Recurrence-free survival 1.05 (0.95-1.15); $P=0.28$	"Epidural use is associated with improved survival in patients with nonmetastatic colorectal cancer undergoing resection but does not support an association between epidural use and decreased cancer recurrence."	Study group variations
Day et al, 2012[81]	Retrospective cohort	Colorectal	GA vs combined GA/EA vs spinal anesthesia	251	173	NA, but trend toward no benefit	"There appears to be no significant advantage to be gained in overall or disease-free survival with the use of regional analgesia compared with opioid analgesia after laparoscopic colorectal resection."	Not controlled
Gottschalk et al, 2012[69]	Retrospective cohort	Malignant melanoma	GA and opioid analgesia vs spinal anesthesia	52	221	NA, but trend toward survival benefit	"These data suggest an association between anesthetic technique and cancer outcome in MM patients after lymph node dissection."	Differing intraoperative and postoperative factors

Table 1. Continued

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Lai et al, 2012[82]	Retrospective cohort	Hepatocellular carcinoma	GA vs combined GA/EA vs spinal anesthesia	62	117	Recurrence-free survival 4.31 (2.24-8.29); $P<0.001$	"Treatment of small HCC by RA under GA is associated with reduced risk of cancer recurrence. No effect of anesthetic technique on overall survival is detected."	Small sample size
Binczak et al, 2013[83]	Retrospective cohort	Colorectal	GA vs combined GA/EA	69	63	Recurrence-free survival 1.24 (0.79-1.93); $P=0.35$	"No clear benefit of regional anesthesia, but a trend to partially positive results was observed."	Small study size Different tumor stages No control group
Holler et al, 2013[84]	Retrospective cohort	Colorectal	GA vs combined GA/EA	442	307	Overall survival 0.73 (CI: NA); $P<0.02$	"The survival benefit with peridural analgesia was greater in patients who had greater medical morbidity."	Different tumor stages
Lacassie et al, 2013[85]	Prospective cohort	Ovarian (stage 3C-4)	GA vs combined GA/EA	37	43	Overall survival 0.74 (0.36-1.49); $P=0.40$	"We found no benefit in overall survival or time to recurrence in patients with advanced stages of ovarian cancer after the use of EA during and after tumor debulking surgery."	Not randomized Advanced stage of cancer No control group Differences in study groups
Merquiol et al, 2013[86]	Retrospective cohort	Head and neck	GA vs combined GA/EA	111	160	Overall survival 0.61 (0.39-1.28); $P=0.03$ Recurrence-free survival 0.49 (0.25-0.96); $P=0.04$	"Association between cervical EA and increased cancer-free survival found in this retrospective study should be an important hypothesis to further investigate."	Small sample size
Wuethrich et al, 2013[73]	Retrospective cohort	Prostate (stage pT3-T4)	GA vs combined GA/EA	67	81	Overall survival 1.16 (0.63-2.17); $P=0.77$ Biochemical recurrence-free survival 1.17 (0.41-3.29); $P=0.61$	"GA with EA was associated with reduced risk of clinical cancer progression."	Short follow-up period Advanced stage

Table 1. Continued

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Roiss et al, 2014[87]	Retrospective cohort	Prostate	GA alone vs combined GA/spinal anesthesia	3,047	1,725	Overall survival 0.90 (0.5-1.6); *P*=0.70 Biochemical recurrence-free survival 1.09 (0.85-1.41); *P*=0.50 Metastasis-free survival 1.11 (0.54-2.27); *P*=0.80	"Spinal anesthesia leads to a complete motor and sensory blockade, supposedly leading to a more effective reduction of surgical stress. . . .Our results strongly argue against an impact of regional anesthesia."	Differences in blood loss Anesthetic technique
Scavonetto et al, 2014[88]	Retrospective cohort	Prostate	GA vs combined GA/EA	1,642	1,642	Overall survival 1.32 (1.00-1.74); *P*=0.05 Biochemical recurrence 1.07 (0.83-1.21); *P*=0.98	"After adjusting for adjuvant hormonal and radiation therapy up to 90 days after surgery, patients receiving GA alone had increased risk of prostate cancer progression compared with those who received GA combined with neuraxial anesthesia."	Open surgical technique Positive operative margins
Sprung et al, 2014[89]	Retrospective cohort	Prostate	GA vs combined GA/EA	486	486	Cancer recurrence 0.79 (0.60-1.04); *P*=0.09	"Compared with GA with systemic opioids, EA and analgesia with fentanyl were not associated with improvement in oncologic outcomes in patients undergoing radical prostatectomy for cancer."	Differing frequencies of postoperative hormonal treatment
Tseng et al, 2014[90]	Retrospective cohort	Prostate	GA vs combined GA/EA	1,166	798	Biochemical recurrence-free survival 1.10 (0.85-1.42); *P*=0.46	"The absence of a positive association between prostate cancer recurrence and spinal anesthesia in our study suggests that the relationship between neuraxial anesthesia and prostate cancer may have more facets. . .including the contribution of postoperative analgesia or other intraoperative factors."	Relatively low rate of biochemical recurrence compared to other studies in control arm

Table 1. Continued

Study	Study Type	Tumor Type	Intervention	RA	GA	Hazard Ratio (95% Confidence Interval)	Conclusions/Relevant Findings	Limitations
Heinrich et al, 2015[91]	Retrospective cohort	Esophageal	GA vs combined GA/EA	118	35	NA, but trend toward no benefit	"We found significantly increased. . .duration of ICU hospitalization (10.1 vs 5.9 days, $P<0.05$) in the non-epidural group compared with the epidural group. However, there were no significant differences in cancer recurrence (23% non-epidural group, 27% epidural group), 1-year mortality (14% vs 11%), or 5-year survival (29% vs 28%) between the two patient groups."	Duration of epidural use Epidurals that used different opioids Timing of epidural
Starnes-Ott et al, 2015[92]	Retrospective cohort	Breast	GA vs paravertebral regional block with GA	193	165	Recurrence-free survival 1.84 (0.34-10.08); $P=0.53$	"The paravertebral regional block with GA group contained advanced stages of disease and had longer surgical procedures than the generalized anesthesia alone group. . . .No association between anesthesia type and recurrence was detected."	Small sample size Short follow-up period

ASA, American Society of Anesthesiologists; CI, confidence interval; EA, epidural anesthesia; FiO_2, fractions of inspired oxygen; GA, general anesthesia; HCC, hepatocellular carcinoma; ICU, intensive care unit; MM, malignant melanoma; NA, not available; RA, regional anesthesia; RRP, retropubic radical prostatectomy.

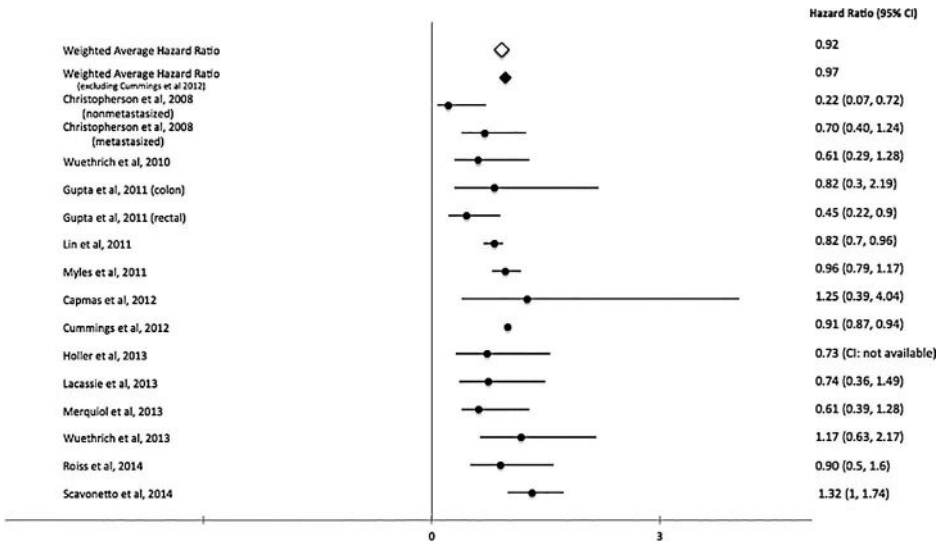

Figure 2. Pooled and individual study hazard ratios for overall survival.[68,72,73,76-80,84-88]

We found only 1 study that suggested a worse outcome with use of RA compared to GA. In a retrospective study, Lai et al compared the use of GA vs epidural anesthesia in patients undergoing radiofrequency ablation to treat hepatocellular carcinoma.[82] Their analysis suggested that treatment of hepatocellular carcinoma by radiofrequency ablation under GA is associated with reduced risk of cancer recurrence, but the authors found no effect of anesthetic technique on overall survival.[82] However, this study is different from all the above studies in that it was evaluating hepatocellular carcinoma, which is pathologically different from colorectal cancer.[82]

Prostate Cancer

Survival outcomes in patients with prostate cancer are not clear because many patients live for extended periods after diagnosis. As a result, many studies involving prostate cancer use biochemical recurrence as the endpoint, and those that use overall survival should use dual study arms to compare outcomes accurately. Biochemical recurrence is defined as either an increase of prostate antigen from its postoperative nadir or $>$0.2 ng/mL.[73] Biochemical recurrence is not a perfect endpoint because it does not translate into cancer-specific survival.[94] In addition, many studies focus on cancers in the advanced stages to help discern the survival benefit. No randomized trials are available, and the identified studies are mostly observational and retrospective.

We identified 3 studies that showed benefits in different markers of clinical significance. Biki et al found that in patients undergoing open prostatectomy surgery with GA, substitution of postoperative opioids with epidural analgesia was associated with a 57% reduction in biochemical cancer recurrence (95% confidence interval [CI] 17%-78%).[29] In a small observational study of 261 patients with approximately 50% having invasive disease, Wuethrich et al found that epidural analgesia resulted in better clinical progression-free survival but only found a small difference in biochemical recurrence-free survival and no difference in overall survival.[72] However, the study was underpowered to detect small changes, and the *P* values were high (P=0.19 for overall survival). Of note, patients in the GA group were given

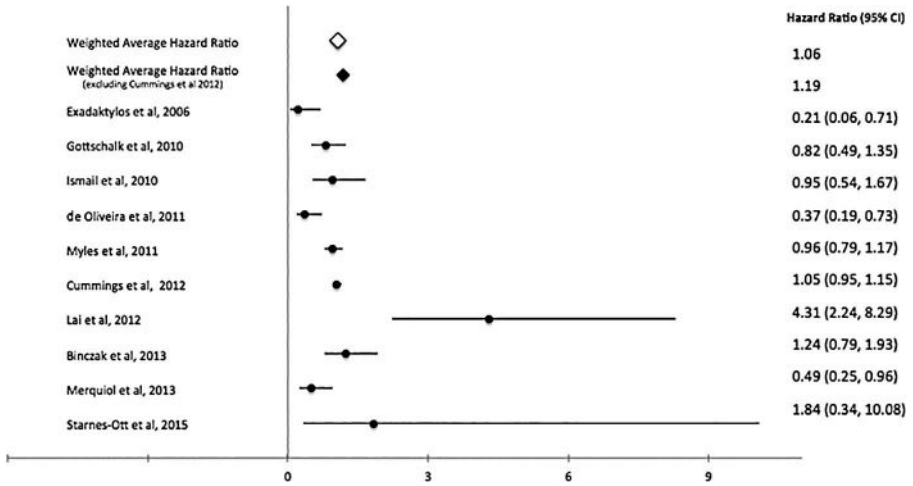

Figure 3. Pooled and individual study hazard ratios for recurrence-free survival. [55,67,70,74,78,80,82,83,86,92]

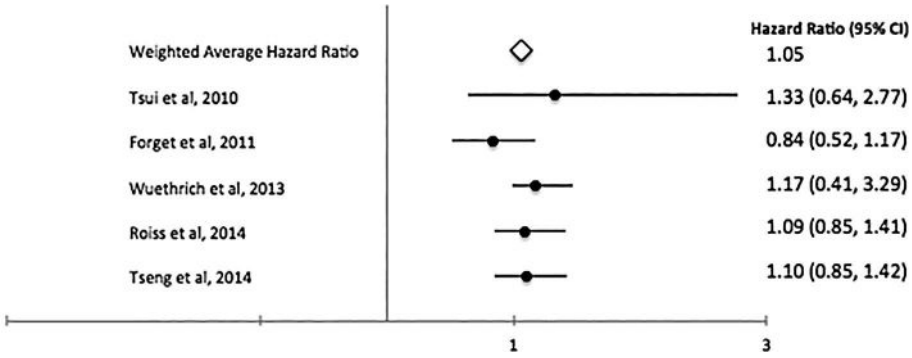

Figure 4. Pooled and individual study hazard ratios for biochemical recurrence-free survival.[71,73,75,87,90]

ketorolac every 8 hours, which may have confounded results.[72] COX inhibitors have been shown to induce apoptosis in prostate cancer cell lines.[23] In a matched study, Scavonetto et al found benefit in the use of epidural analgesia via decreased systemic progression of the cancer and improved overall survival.[88] Further, although not statistically significant on a multivariate analysis, prostate cancer death was also reduced with RA.[88]

We identified 6 studies that showed no benefit for RA in prostate cancer surgery. Tsui et al found no difference between epidural and control groups in disease-free survival at a median follow-up time of 4.5 years in their secondary analysis of patients undergoing radical prostatectomy.[71] In another study, Wuethrich et al found no difference in biochemical recurrence-free, local and distance recurrence-free, and overall survival in patients with invasive prostate cancer undergoing radical prostatectomy with combined GA and epidural analgesia or GA alone.[73] However, Wuethrich et al found a reduced risk of clinical cancer progression.[73] As in the Tsui et al study,[71] patients in the GA group in the Wuethrich et al study received ketorolac, which may have confounded the results.[73] In a study of 1,111 patients undergoing radical prostatectomy, Forget et al found no significant association between epidural analgesia and risk of cancer relapse.[75] Furthermore, the authors found an increased risk associated with the use of intravenous sufentanil with an HR of 7.78 (95% CI 5.79-9.78). However, the follow-up time in this study was fairly short, approximately 3 years, and patients often received multimodal analgesia, which made individual evaluation challenging.[75] Another large study (4,772 patients) by Roiss et al compared patients undergoing radical prostatectomy with either GA alone or GA with spinal anesthesia and found no difference in overall survival or biochemical recurrence-free survival.[87] However, this study used propensity-scoring matching because of differences in prostate specific antigens, tumor grades, and histology.[87] Similarly, Sprung et al found no benefit with the use of epidural analgesia.[89] Sprung et al performed neuraxial analgesia without utilizing volatile anesthetics. Volatile anesthetics have been thought to affect cancer recurrence because of their inhibition of NK cells. Despite this theoretical association, no differences in outcomes were seen. Tseng et al used spinal anesthesia to look for potential cancer or non–malignancy-associated benefits for radical prostatectomy.[90] The authors found no benefit in biochemical recurrence after a 4- to 5-year follow-up period.[90]

Breast Cancer

Exadaktylos et al performed one of the first studies evaluating the benefit of neuraxial anesthesia.[67] In a retrospective analysis of 129 patients with breast cancer who underwent mastectomy, the researchers found that paravertebral anesthesia and analgesia for breast cancer surgery reduced the risk of recurrence or metastasis during the initial 3 years of follow-up compared to GA alone.[67] The authors found no significant differences between the 2 study arms. The recurrence-free survival rate was 94% (95% CI 87%-100%) in patients who received paravertebral analgesia compared to 82% (95% CI 74%-91%) in GA patients at 24 months.[67] At 36 months, this difference became more pronounced with a recurrence-free survival of 94% (95% CI 87%-100%) in patients who received paravertebral analgesia and 77% (95% CI 68%-87%) in patients who did not receive paravertebral analgesia.[67] However, in another retrospective study, Starnes-Ott and colleagues found that in a group of 358 patients, anesthetic choice did not result in a significant difference in recurrence-free survival at the 28-month mark.[92] Despite the similar outcome, the paravertebral block group included patients with more advanced stages of cancer, more invasive treatments, longer surgery times, and decreased body mass index (BMI) compared to the GA group.[92] BMI has been associated with increased risk of recurrence and death from cancer.[95] These differences may confound the results. Schnabel et al published a metaanalysis of RCTs analyzing efficacy and safety of paravertebral blocks for breast cancer surgery.[96] They concluded that a reduced need for postoperative morphine among the group of patients undergoing surgery with paravertebral block correlated with a lower recurrence of breast cancer.[96]

Because of benefits in terms of overall survival, a large multicenter, international trial (NCT00418457) is underway in patients with stage I-III breast cancer undergoing mastectomy with or without axillary dissection.[97] While this trial may take years to complete, some of the initial data based on tissue samples have shown promise. Early clinical results from Wu et al show an analgesic benefit in patients undergoing breast cancer surgery.[98] RA compared with GA resulted in a greater percentage decrease in postoperative compared to preoperative concentrations of IL-1B (pro-inflammatory), an increase in the concentrations of IL-10 (antiinflammatory), and an attenuation in MMPs involved in tumor migration and metastasis.[20] Deegan et al showed that paravertebral anesthesia alters some of the proinflammatory

Table 2. Pooled Weighted Hazard Ratios for All Cancers and by Cancer Type

Type of Cancer	Weighted Average Hazard Ratio
All cancers	
Overall survival[68,72,73,76-80,84-88]	0.92
Recurrence-free survival[55,67,70,74,78,80,82,83,86,92]	1.06
Biochemical recurrence-free survival[71,73,75,87,90]	1.05
Gastrointestinal cancer	
Overall survival[68,76,78,80,84]	0.91
Recurrence-free survival[55,78,80,82,83]	1.05
Prostate cancer	
Overall survival[72,73,87,88]	1.06
Biochemical recurrence-free survival[71,73,75,87,90]	1.05
Breast cancer	
Recurrence-free survival[67,92]	1.41
Ovarian cancer	
Overall survival[77,79,85]	0.94

cytokines involved in regulating perioperative cancer immunity.[99] In addition, the authors found reduced proliferation of the cancer cell line associated with the use of RA.[99] In a study by Desmond et al, excised breast cancer specimens from the RA group demonstrated increased infiltration of NK and Th cells compared to the GA group.[100] Further, RA has been shown to lead to a smaller increase in VEGF-C compared to GA.[101] VEGF-C has been shown to promote angiogenesis and can be overexpressed in breast cancer.[101]

Ovarian Cancer

We identified 4 retrospective studies that compared the effects of RA and GA in patients with ovarian cancer. Lin et al[77] and de Oliveira et al[74] found a benefit from the intraoperative use of epidural anesthesia compared to GA. Lin et al, in a sample of 143 patients, found that 3-year and 5-year overall survival rates were 79% and 61% in the epidural group compared to 58% and 49% in the GA group, respectively.[77] After adjusting for various factors such as carcinoma antigen 125 (CA-125) concentration, histology, residual tumor, and lymphatic metastasis, GA was associated with an HR of 1.214 (95% CI 1.075-1.431, P=0.043).[77] De Oliveira et al, in a sample of 182 patients, found that the group with intraoperative and postoperative epidural use had a significantly greater time to recurrence compared with the GA group.[74] Further, the intraoperative epidural group also had an increased mean time to death compared with the GA and postoperative epidural group (mean time 96 months in the intraoperative epidural group vs 71 months and 70 months in the postoperative nonepidural group and in the postoperative epidural group, respectively).[74]

Other studies have found no benefit for cancer recurrence. In a group of 94 patients with advanced ovarian cancer, Capmas et al found no improvement in overall survival or recurrence-free survival with the use of postoperative RA.[79] Further, roughly 44% of patients in the Capmas et al study received blood transfusions, which has been shown to increase the risk of recurrence.[79] Lacassie et al evaluated a group of 80 patients matched using propensity scoring and also found no benefit in overall survival or time to recurrence.[85]

Other Cancers

RA has also been studied in other cancers including malignant melanoma, cervical cancer, and laryngeal cancer. In a retrospective review of 4,329 patients, Schlagenhauff et al found that RA is associated with longer survival in surgeries associated with malignant melanoma compared to GA.[102] Further, Gottschalk et al found a nonsignificant trend toward longer overall survival in patients undergoing spinal anesthesia (96 vs 70 months, P=0.087).[69] Ismail et al found no benefit in the use of epidural analgesia in patients undergoing brachytherapy for cervical cancer.[70] In contrast to open surgery, brachytherapy involves less tissue manipulation and shorter procedure duration, factors that can affect cancer recurrence.[70]

Merquiol et al, evaluating a group of 271 patients undergoing surgery for laryngeal and hypopharyngeal cancer, found that combined GA and epidural anesthesia with postoperative epidural analgesia resulted in significantly improved cancer-free survival and overall survival.[86]

LIMITATIONS

This study has multiple limitations, the most important being that many of the studies included are retrospective. While some of these studies used several factors to match patients in the study arms, some factors may still be unaccounted for. In studies that evaluate cancers in advanced stages, the mortality rate is high at baseline. Consequently, defining overall survival and measuring recurrence-free survival or biochemical recurrence-free survival in these populations can be difficult. Patients with advanced-stage cancer have a high likelihood of dying from diseases that are secondary to the cancer but not directly attributable to the cancer, limiting the ability to calculate survival benefits. In studies that use recurrence as the primary outcome, different criteria are often used to define recurrence. Many types of recurrence exist, and comparing the different types can be challenging. Some types of

recurrence are not associated with overall survival, diminishing its prognostic value. Further, many studies evaluate patients during a period of time that is too short to reach significant conclusions. Numerous studies lacked significant power to draw strong conclusions. Some studies included in this analysis were performed on particular populations, so translating some of these findings to the general population may be challenging. Finally, in some studies, patients received multimodal analgesia, which made evaluating the analgesia techniques individually especially challenging.

CONCLUSION

RA has been shown to have no overall benefit in overall survival, recurrence-free survival, and biochemical recurrence-free survival. However, numerous individual studies have shown some benefit, and results have been controversial. Different mechanisms have been proposed to explain this benefit but none has been proven. Thus, more work is needed to critically evaluate the role of RA in a prospective, randomized fashion. Clinical trials are underway across the world to evaluate the impact of RA. RA has the potential to alter the way cancer pain is managed and could significantly impact morbidity and mortality.

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