Regional anesthesia/analgesia and the risk of cancer recurrence and mortality after prostatectomy: a meta-analysis

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Practice points

- Regional anesthesia/analgesia has sparing opioid effects.
- Local anesthetics have anti-inflammatory and immune protective effects.
- Both, sparing opioid and anti-inflammatory effects have been proposed to be the mechanisms by which regional anesthesia might prolong the survival of cancer patients.
- Regional anesthesia/analgesia has shown to reduce cancer recurrence in some retrospective studies but not in other similar clinical reports.
- The findings of this study do not support the association between regional anesthesia/analgesia and improved recurrence-free survival after radical prostatectomy.
- Regional anesthesia/analgesia is associated with a better overall survival after radical prostatectomy.

Aims: To determine whether the use neuraxial anesthesia/analgesia is associated with longer biochemical recurrence-free survival (BRFS) and overall survival (OS) after radical prostatectomy. **Methods:** Ten studies were included in the meta-analysis. A random-effects model was used to estimate the hazard ratios (HRs). **Results:** The HR for BRFS was 1.02 (95% CI: 0.91–1.15) for all studies and 1.08 (95% CI: 0.91–1.15) for those that included propensity score matching. For OS, the HR across all studies was 0.91 (95% CI: 0.7–1.15) and 0.81 (95% CI: 0.68–0.96; $p = 0.016$) for those reporting propensity score matching. **Conclusion:** The anesthetic technique used during oncologic prostatectomy surgery is not associated with longer BRFS. By contrast, the use of regional analgesia appears to improve OS.

Prostate cancer is the most common malignancy and the second leading cause of cancer death in males [1]. Radical prostatectomy (RP) has been shown to decrease mortality and is the treatment of choice in many patients with localized cancer [2]. However, ~25% of patients still develop local recurrence or distant metastasis after primary tumor resection [3]. Recurrences are related to tumor stage, Gleason score, lymph node stage, surgical margin status and preoperative serum prostate-specific antigen level [4,5].

KEYWORDS

• biochemical recurrence-free survival
• overall survival • prostate cancer • regional anesthesia

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In recent years, it has been suggested that tumor growth might be facilitated by surgical stress, volatile anesthetics, opioids analgesics and blood transfusion, which can all occur during RP. First, surgical stress produces activation of the sympathetic nervous system followed by an increase of circulating catecholamines that act on adrenergic receptors of macrophages with prometastatic activity [6]. Opioids possess an inhibitory effect on both humoral and cellular immune responses and have proangiogenic effects that have been linked to cancer cell proliferation [7,8]. Furthermore, opioids have been shown to facilitate prostate cancer dissemination in patients with high expression of μ -receptors in their histological specimens [9].

Due to the opioid-sparing and sympathetic and immune modulatory effects of regional anesthesia/analgesia, an increasing interest has arisen to evaluate whether neuraxial techniques (spinal and epidural) could improve survival outcomes after oncological surgery. A recently published meta-analysis conducted by Chen and Miao [10] failed to show an association between the use of regional anesthesia/analgesia and improved cancer-specific survival. Considering the fact that this study included different cancers and that recurrence rates and patterns of different cancers vary, the results were biased by this important tumor behavior heterogeneity. Therefore, the objective of the current study was to conduct a meta-analysis to evaluate the effect of neuraxial anesthesia/analgesia in combination with general anesthesia or alone on biochemical recurrence-free survival (BRFS) or clinical recurrence-free survival (RFS), and overall survival (OS) after open RP.

Methods

• Literature search strategy

Systematic literature search strategies were devised for the MEDLINE and EMBASE databases by a research librarian (GP) following the PICO (population, intervention, comparison and outcome) format: (P) prostate cancer patients undergoing surgery/prostatectomy, (I) regional anesthesia/analgesia, (C) general anesthesia or administration of regional analgesia intraoperatively/postoperatively and (O) survival or disease progression. Terms used for each concept included both keywords and controlled vocabulary (i.e., MeSH or Emtree) descriptors. To insure high sensitivity, search strategies were validated for completeness using

a pool of known relevant studies. The literature search included all retrospective cohort studies and randomized controlled trials (if any). We considered only studies that included adult patients (>18 years old) who underwent open prostatectomy for treatment of prostate cancer. We excluded all case reports and cohort studies that did not clearly describe the intra- or post-operative anesthetic and analgesic technique nor BRFS, RFS or OS. We also excluded studies in which prostatectomy was done as part of treatment for other cancers (i.e., bladder cancer). The primary outcomes of the study were RFS (defined as BRFS or clinical RFS) and OS. Results were limited to English language, 1970–2014 (September 23), and animal-only studies were eliminated. Three authors (JP Cata, BM Lee and VS Gothra), independently examined titles and abstracts to remove irrelevant reports. We identified and linked multiple reports of the same study, and we excluded them if duplicated or not relevant. Publication bias was addressed by including trial databases in the electronic search, looking for published, unpublished and ongoing trials. We planned to contact the authors to ask for results, if unpublished trials were found in the literature search. Multiple publication bias was addressed by combining reports that described different findings from the same study, and by excluding papers that reported results that had already been published.

• Study quality assessment & selection

The quality of the studies was evaluated using the Newcastle–Ottawa scale (NOS) [11]. The scale consists of eight items that cover three aspects: selection (representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study); comparability of cohorts on the basis of the design or analysis; and outcome (assessment of outcome, length of follow-up, adequacy of follow-up of cohorts). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. A maximum score is nine points, and a score ≥ 6 is considered to indicate high quality, while a score < 6 indicates low quality. Study quality assessments, using the NOS, were conducted independently by (BM Lee and V Singh Gothra) and then reassessed by (JP Cata) to resolve inconsistencies.

• Statistical analysis

Studies with a NOS lower than six were excluded from the statistical analysis. For each study we examined, the hazard ratio (HR) was used as the primary measure of association. Several of the studies employed propensity score matching in their analyses. In those instances where estimates using matching were provided, we ran a separate analysis that would provide the combined estimate across all studies using only estimates emanating from the matched analysis. Although computed values for Cochran's Q test and Higgin's I^2 were used to assess between study heterogeneity, we employed random-effects models in all cases to estimate the combined HR association across studies. The method of DerSimonian and Laird [12] was used, where the weight for each study was provided by the inverse of the standard error for the natural log of the HR estimate. Analyses were conducted for both RFS and OS. Where studies presented results at multiple time points during follow-up (e.g., RFS

at 3, 5 or 10 years), we only included the longest follow-up from each study to avoid the risk of multiplicity of analysis. We intended to explore heterogeneity by subgroup analysis (i.e., studies that included matched and/or nonmatched analysis of the data). Graphical representations of the results were displayed using forest plots generated with Stata, version 13.0, statistical software (StataCorp LP, College Station, TX, USA).

Results

• Included studies

The literature search resulted in 30 relevant articles (Figure 1). After screening abstracts and reviewing full-text manuscripts, ten studies that met the inclusion criteria were considered in the meta-analysis (Table 1). One study was excluded because of a low NOS score. All included studies were retrospective and included in total 6261 patients in the general anesthesia only group and 7504 patients in the neuraxial anesthesia

Figure 1. Literature search diagram. The flow diagram depicts the literature search process and selection of studies included in the meta-analysis.

NOS: Newcastle–Ottawa scale.

Table 1. Description of the studies included in the meta-analysis.

Authors	Year	Anesthetic technique	Neuraxial (n)	GA (n)	Median follow-up (years) [†]	Outcomes	Findings	Study quality [‡]	Ref.
Biki <i>et al.</i>	2008	Epidural + GA vs GA	102	123	9	RBFS	Improved BRFS	8	[14]
Tsui <i>et al.</i>	2009	Epidural + GA vs GA	49	50	4.5	RBFS	No difference	7	[15]
Wuethrich <i>et al.</i>	2010	Epidural + GA vs GA	103	158	11.9 vs 8.5	RBFS/OS/ PFS/CSS	Improved PFS	8	[16]
Forget <i>et al.</i>	2011	Epidural + GA vs GA	578	533	3.16	RBFS	No difference	8	[17]
Wuethrich <i>et al.</i>	2013	Epidural + GA vs GA	67	81	14	RBFS/OS/ PFS/CSS	No difference	8	[18]
Scavonetto <i>et al.</i>	2013	Spinal/ epidural + GA vs GA	1642	1642	8.6 vs 9	RFS/OS/ PFS/CSS	Improved PFS and OS	9	[19]
Roiss <i>et al.</i>	2014	Spinal + GA vs GA	3047	1725	5	RBFS/ MFS/OS	No difference	9	[20]
Tseng <i>et al.</i>	2014	Spinal vs GA	1166	798	15	RBFS	No difference	9	[21]
Sprung <i>et al.</i>	2014	Epidural vs GA	486	486	16.2 vs 15.1	RFS/OS/ PFS/CSS	No difference	9	[22]
Ehdaie <i>et al.</i>	2014	Spinal vs GA	264	665	4.6	BRFS	No difference	8	[23]

[†]Some studies reported a median follow-up for each group, others reported one median follow-up value for both groups.
[‡]Evaluated using the Newcastle–Ottawa scale.
 BRFS: Biochemical recurrence-free survival; CSS: Cancer-specific survival; GA: General anesthesia; MFS: Metastasis-free survival; OS: Overall survival; PFS: Clinical progression-free survival; RFS: Recurrence-free survival.

group. Seven studies compared effects of combined neuraxial analgesia and general anesthesia versus general anesthesia only. The other three studies compared patients who had neuraxial anesthesia only versus those who received general anesthesia only. As far as the neuraxial blockade is concerned, six studies involved epidurals whereas three studied spinal anesthesia. In one study by Scavonetto *et al.* [13], 83% of the neuraxial anesthesia group were spinal anesthesia and 17% were epidural.

BRFS was reported in all studies, except Sprung *et al.* [24] and Scavonetto *et al.* [13] who reported cancer recurrence as biochemical, local or systemic recurrence. Studies by Biki *et al.* [25], Tsui *et al.* [19], Forget *et al.* [22], Tseng *et al.* [14] and Ehdaie *et al.* [15] provided estimates from an unmatched group of patients. Scavonetto *et al.* [13], Sprung *et al.* [24] and Roiss *et al.* [17] reported HR obtained after matching patients. Both studies from Wuethrich *et al.* [21,23] provided estimates from matched and unmatched patient populations of patients. Regarding OS, only five studies that reported OS were included in the analysis.

• Recurrence-free survival

Ten studies were included in the analysis. Low heterogeneity was detected when all studies ($I^2 = 24.8\%$; $p = 0.215$) or those that used propensity score matching ($I^2 = 0\%$; $p = 0.698$) were included in the analysis. The combined HR was 1.02 (95% CI: 0.91–1.15; $p = 0.750$), indicating no difference in the risk of a biochemical recurrence for regional anesthesia/alone or in combination with general anesthesia only relative to anesthesia general anesthesia only (Figure 2A). The analysis of the studies that had used propensity score matching showed an HR of 1.08 (95% CI: 0.96–1.21; $p = 0.182$), thus indicating a slight, but not statistically significant, increase in the risk of recurrence for general anesthesia only relative to anesthesia/analgesia alone or in combination with general anesthesia (Figure 2B).

• Overall survival

The Figure 3A shows that the combined HR for OS across all studies was 0.90 (95% CI: 0.70–1.15; $p = 0.390$) indicating that patients receiving regional anesthesia/analgesia alone

Figure 2. Biochemical recurrence-free survival: neuraxial analgesia/anesthesia ± general anesthesia versus general anesthesia only. (A) Studies by Biki, Tsui, Forget, Wuethrich, Tseng and Ehdaie *et al.* provide estimates from a multivariable Cox regression model. All other studies have HR obtained from a matched analysis. Recurrence-free survival was reported in all studies, except Scavonetto and Sprung that reported tumor recurrence as biochemical, local or systemic recurrence. (B) All studies have HR obtained from a matched analysis. Recurrence-free survival was reported in all studies, except Scavonetto and Sprung that reported tumor recurrence as biochemical, local or systemic recurrence.

D + L: Dersmonian and Laird; HR: Hazard ratio; I-V: Random effect.

Figure 3. Overall survival: neuraxial analgesia/anesthesia ± general anesthesia versus general anesthesia only. All studies had HR estimates obtained from a matched analysis. **(A)** All studies. **(B)** Studies showing propensity score matching. D + L: Dersmonian and Laird; HR: Hazard ratio; I-V: Random effect.

or combination with general anesthesia had a 10% lower risk of mortality relative to patients receiving general anesthesia only. The analysis indicated moderate heterogeneity ($I^2 = 35.7\%$, $p = 0.183$). Using only those studies that had used propensity score matching, the combined HR of 0.81 (95%CI: 0.68, 0.96; $p = 0.016$) was statistically significant, and showed a 19% reduction in the risk of mortality for patients receiving regional anesthesia/analgesia alone or in combination with general anesthesia versus those who had general anesthesia only. Remarkably, low heterogeneity was found ($I^2 = 0\%$; $p = 0.686$) (Figure 3B).

Discussion

The present meta-analysis showed that the use of regional anesthesia alone or in combination with general anesthesia for RP is associated with longer OS compared with general anesthesia alone. Although, the results of this meta-analysis are in line with previously published studies indicating an association between the use of epidural anesthesia and/or analgesia and improved short- and long-term OS; a recent study suggests in fact the opposite [16,18,20]. It has been suggested that regional anesthesia might improve the short-term survival of patients by reducing pulmonary complications, decreasing deep venous thrombosis/pulmonary embolism and lowering rate of blood transfusions; however, it remains less clear why the use of that anesthesia technique might reduce long-term mortality [16,20,26–27].

Our study also demonstrated that the use of epidural anesthesia/analgesia did not improve RFS (measured as biochemical-free survival) after RP. Preclinical and clinical studies indicate that regional anesthesia and analgesia can preserve a healthy immune system [7,28–30]. In patients undergoing oncological surgery, the importance of an effective immune system response during the perioperative period relies in the fact that an intact immunological response is necessary to avoid minimal residual disease proliferation after surgery and during the time between the surgery and the start of postoperative adjuvant therapy [7]. Opioids are commonly given intra- and postoperatively to provide analgesia in patients who undergo open RP. It has been suggested that opioids can favor tumor growth by two mechanisms. First, they can induce immune suppression and second, stimulate the proliferation of prostate cancer metastasis. Zylla *et al.* demonstrated that patients with

advanced prostate cancer who showed high levels of μ -receptors expressed in the prostate cancer specimens had lower survival than those who expressed lower levels of the receptor, highlighting the impact of exogenous opioids in prostate cancer invasion and growth [9].

Several comments can be made about the studies included in our meta-analysis. For instance, Biki *et al.* [25] were the first to report an association between epidural anesthesia and a longer BRRS. However, that study presented several limitations including a small sample size ($n = 225$), nonrandomized anesthetic technique assignment and no propensity score matching analysis. Wuethrich *et al.* [21] initially published that the use of combined general and epidural anesthesia was also associated with a reduced risk of cancer progression. But a later work conducted by the same authors and included longer patient follow-up after surgery (14 years) could not confirm their earlier published results [23].

A large retrospective study by Scavonetto *et al.* [13] demonstrated the combination of general and neuraxial anesthesia also reduced cancer progression. However, in a more recent study, the same authors reported no improvement in oncologic outcomes with the use of epidural anesthesia and analgesia only compared with general anesthesia only [24]. It is worth mentioning that these two studies differed in the type of opioid administered neuraxially. In one study, patients receiving general anesthesia supplemented with neuraxial hydrophilic opioids (i.e., morphine), whereas in the second study, fentanyl was injected in the epidural space. The authors argued that the difference in the results between the two studies was mainly due to the fact that prolonged infusion of epidural fentanyl has systemic effect. Considering the fact that the use of general anesthesia in both groups of patients is a confounding factor in the effect of neuraxial analgesia/anesthesia on oncologic outcomes, Sprung *et al.* [13], Tseng *et al.* [14] and Ehdaie *et al.* [15] compared in their studies patients receiving neuraxial anesthesia only versus those receiving general anesthesia only. None of them have found a significant difference in RFS or OS. Roiss *et al.* [17] conducted the largest retrospective study where they analyzed 4772 patients who underwent open prostatectomy through highly standardized surgical and anesthetic procedures, and calculated statistical estimates using propensity score matching. No difference between the two groups in terms

of RFS and metastasis-free survival. Similarly, Forget *et al.* [22] reported no association between epidural anesthesia and better oncologic outcomes; however, they identified a negative effect of intraoperative sufentanil on RFS.

The present work is a meta-analysis based on retrospective studies, and as such, it is subject to several limitations. First, retrospective studies are influenced by confounding variables (such as different definitions of RFS), unmeasured factors and the fact that one-third of the results were derived from only one study. A low degree of heterogeneity and the use of a random-effects model rather than a fixed-effect model to analyze the data is strength of this study; however, it is important to note that our findings could be still highly influenced by different surgical and anesthesia techniques, varying long-term follow-up, different baseline characteristics and endpoints among the different studies [31]. Although, our analysis included patients from ten different studies, it is worth mentioning that studies by Scavonetto *et al.* and Sprung *et al.* did not reported BRFS which might confound our results. Second, we did not compile raw data from each study. Our results could have been influenced by the possibility of errors in reporting and lack of information from each patient included in the studies used in the meta-analysis; therefore, outcome reporting bias assessing the risk of bias from within-study selective reporting and selective under-reporting of data was not performed. Third, we did not address language bias because we only included studies published in English language. Fourth, our findings are only applicable to a population of patients that has decreased over the last years since laparoscopic prostatectomies are being performed with more frequency in the USA and Europe. And last, we only included studies that defined recurrence as a rise in the prostate-specific antigen. This is the most sensitive tool

for detecting recurrence after prostatectomy; however, it cannot distinguish between local, regional or distant recurrence. Unfortunately, not all studies included in our search reported the type of recurrence.

Conclusion

In conclusion, this meta-analysis shows no association between type of anesthesia/analgesia and oncologic outcomes and BRFS in patients with prostate cancer undergoing open RP. Interestingly, we found that the risk of mortality is significantly reduced with the use of regional anesthesia. Prospective randomized controlled trials are needed to properly assess whether there is a causative relation between neuraxial anesthesia/analgesia and a lower risk of cancer recurrence and improved survival.

Future perspective

The beneficial effects of regional anesthesia/analgesia on oncological outcomes such as cancer recurrence remain unknown. In recent years, more information has been published on the potential effect of local anesthetics on inflammation, immune system and cancer cells; therefore, new experimental and clinical studies will be conducted in the near future to elucidate the question of whether regional anesthesia/analgesia cancer prolong survival in patients with cancer.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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