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Original Article

The impact of neuraxial anesthesia on cancer recurrence and survival for patients with prostate cancer: a meta-analysis

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Abstract: Previous studies suggest an association between neuraxial anesthesia and cancer recurrence and survival for patients with prostate cancer. However, conclusions from these studies were controversial. Thus, we examine the association of neuraxial anesthesia (combined with or without general anesthesia (GA)) with prostate cancer recurrence and survival after cancer surgery. Based on the inclusion and exclusion criteria, the association of neuraxial anesthesia with prostate cancer recurrence and survival were searched from various databases including PubMed, Embase, China Biology Medicine disc (CBM), China National Knowledge Infrastructure (CNKI) up to July 10th, 2016 and the meta-analysis was performed with STATA and Review Manager statistical software. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to evaluate the strength of the correlations. Additionally, different subgroup-analyses and a publication bias test were performed. Through a systematic literature search, 7 previous studies were identified and involved in this meta-analysis. Consequently, our evidence indicates no association between neuraxial anesthesia and overall survival (OS) (HR=1.19, 95% CI=0.73-1.94, P=0.474) and recurrence-free survival (RFS) (HR=0.95, 95% CI=0.84-1.08, P=0.426) existed compared to GA. Similarly, no association was detected in different subgroups of RFS. In conclusion, this meta-analysis indicated there was no association between neuraxial anesthesia and prognosis of prostate cancer patient after surgery.

Keywords: Neuraxial anesthesia, overall survival, recurrence-free survival, prostate cancer

Introduction

Prostate cancer (PCa) is the primary cause of cancer-related death which seriously threatens psychological and physical health in male. PCa characterized by high incidence and mortality rate has drawn extensive attention in clinic. An estimation of 2015 cancer statistics revealed 220,800 new patients and 27,540 new deaths assigned to PCa in the United States [1]. Although there are different treatment options for prostate cancer, surgical removal of the primary tumor mainly become the best choice for a significant fraction of patients [2]. However, surgery itself has a potential to promote the development of metastases and reduce survival. After surgery, many patients already harbor micrometastases and scatter tumor cells due to tumor cells into the lymphatic and blood streams at the time of surgery [3, 4]. Whether minimal residual disease leads to local or metastatic recurrence largely depend on the efficacy of host defenses [5]. It is well known that perioperative factors could affect cancer progression of minimal residual disease, such as surgery itself and opioids [6, 7].

Anesthetic technique may contribute to the suppression of cell-mediated immunity by decreasing the activity of natural killer (NK) cells, which are the primary defense against cancer [8]. Recently, several studies have shown that neuraxial anesthesia (including epidural anesthesia or spinal anesthesia) may affect the prognosis of prostate cancer patient after surgery. However, these conclusions from these studies were controversial, which could be explained by the relatively small samples in each published study. Meta-analysis can explore the authentic and comprehensive results through

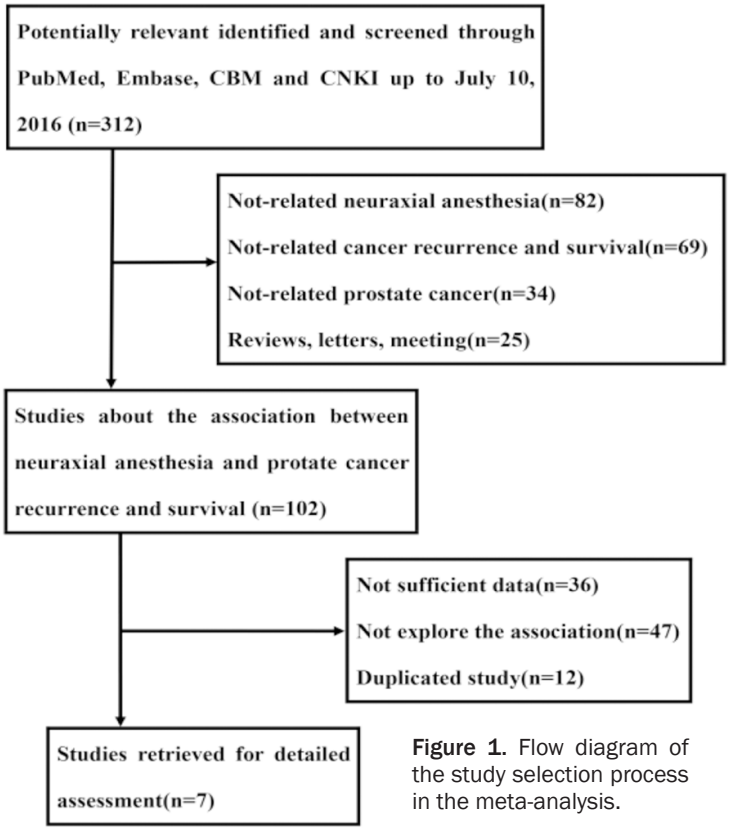

Figure 1. Flow diagram of the study selection process in the meta-analysis.

incorporating all available evidences to get a relatively precise and accurate estimation using statistical software [9]. Herein, our research group conduct a meta-analysis to assess some possible correlations between neuraxial anesthesia and prognosis of prostate cancer, which efforts should hold great promise in the clinical therapy for prostate cancer.

Materials and methods

Identification and eligibility of relevant studies

Literature resources including PubMed, Embase, CBM and CNKI were searched for eligible literatures, using the terms ("anesthetic technique" or "spinal anesthesia" or "epidural anesthesia" or "neuraxial anesthesia", and "prostate cancer" or "prostate carcinoma" or "prostate neoplasm", and "survival" or "recurrence" or "metastasis"). Last search of current investigation was updated on July 10th, 2016. There was no language restrictions. We identified other relevant articles according to scan all retrieved articles and reviews. We treated them independently if the different ethnicities were found in a reported article.

Inclusion criteria

Studies followed the three criteria could be identified: (1) all included studies belonged to case-control or cohort studies; (2) can require relevant available data to evaluate the correlations between neuraxial anesthesia and prognosis of prostate cancer; Studies met the following three criteria were excluded: (1) the available data regarding about associations was absent; (2) similar or duplicate study (When the same or similar cohort was applied, after careful examination, the most complete information was included); (3) other types of articles including reviews or abstracts.

Data extraction

In the light of inclusion and exclusion criteria, we extracted the relevant information from each eligible publication. If disagreements were noticed, we were clearly open to discussion by each other (J. Liu and Y. Fan), or reviewed by a third author (H. Jiang).

The data on first author, publication year, study country, number of case and control, survival, study design and HR (95% CI) were collected by two authors independently. The Newcastle-Ottawa Scale consisted of selection, comparability of the groups and ascertainment of exposure was introduced to evaluate the included publication's quality. The NOS scores 0 to 10 stars. If an included study obtained no less than seven stars, it could be regarded as high-quality [10]. We have not contacted any author of the original researches even though the essential information could not be available. Besides, design type was stratified into two groups: retrospective and prospective. Survivals were mainly divided into OS and RFS.

Statistical analysis

We explored the association of neuraxial anesthesia on prognosis of prostate cancer by applying Review Manager software (RevMan 5, The Cochrane Collaboration, Oxford, UK) and STATA software (Version 12.0, StataCorpotation,

Table 1. Main characteristics of studies regarding the association between neuraxial anesthesia and prognosis of prostate cancer patients

Author	Year	Country	Design type	Survival	Case/control	HR (95% CI)	NOS
Tseng KS [15]	2014	USA	Retrospective	Recurrence free survival	1166/798	0.91 (0.70-1.18)	7
Wuethrich PY [16]	2013	Switzerland	Retrospective	Overall survival	67/81	1.79 (0.95-3.39)	7
				Recurrence free survival		0.58 (0.27-1.29)	
Wuethrich PY [17]	2010	Switzerland	Retrospective	Overall survival	103/158	0.61 (0.29-1.28)	7
				Recurrence free survival		1.14 (0.84-1.54)	
Tsui BC [18]	2010	Canada	Prospective	Disease free survival	49/50	1.33 (0.64-2.77)	6
Forget P [19]	2010	Belgium	Retrospective	Recurrence free survival	578/533	0.84 (0.52-1.17)	7
Biki B [20]	2008	Ireland	Retrospective	Recurrence free survival	102/123	0.43 (0.22-0.83)	6
Scavonetto F [21]	2004	USA	Retrospective	All cause death	1642/1642	1.32 (1.00-1.74)	8
				Recurrence free survival		1.00 (0.83-1.21)	

HR, hazard ratio; CI, confidence interval; NOS, The Newcastle-Ottawa Scale.

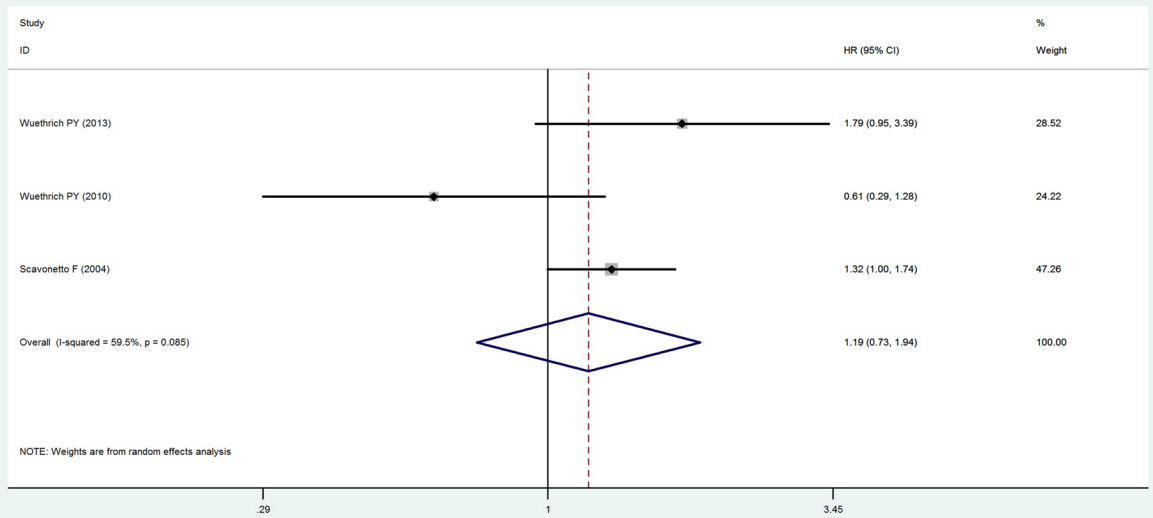

Figure 2. Forest plot for the meta-analysis of the association between neuraxial anesthesia with OS with random-effects model. The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary HR and 95% CI. CI, confidence interval; HR, hazard ratio.

TX). HR and 95% CI were calculated for assessing the relationships between neuraxial anesthesia and prostate cancer prognosis. Hardy-Weinberg equilibrium (HWE) was assessed by χ^2 test in the control group of each study. Meanwhile, the heterogeneity has been assessed via chi-square-based Q and I^2 test across studies (no heterogeneity I^2<25%, moderate heterogeneity I^2=25%-50%, extreme heterogeneity I^2>50%) [11]. In case of extreme heterogeneity (I^2>50% or P<0.01 for Q test), we used random-effects (DerSimonian and Laird method) model [12]. Otherwise, fixed-effects (Mantel-Haenszel method) model was introduced [13].

One-way sensitivity analyses individually removed publications in meta-analysis were conducted to assess results' stability. It mainly explore the impact of specific study upon mixed HR.

The Egger and Begg's funnel plots where logHR was plotted against SE. *P* value less than 0.05 indicated that there was a bias of study [14]. Additionally, different subgroups consisted of study design, sample size and NOS were conducted.

Results

Characteristics of eligible studies

Finally, 7 studies consisted of 3207 cases and 3385 controls satisfied the eligible studies (**Figure 1**) [15-21]. Of these studies, 6 retro-

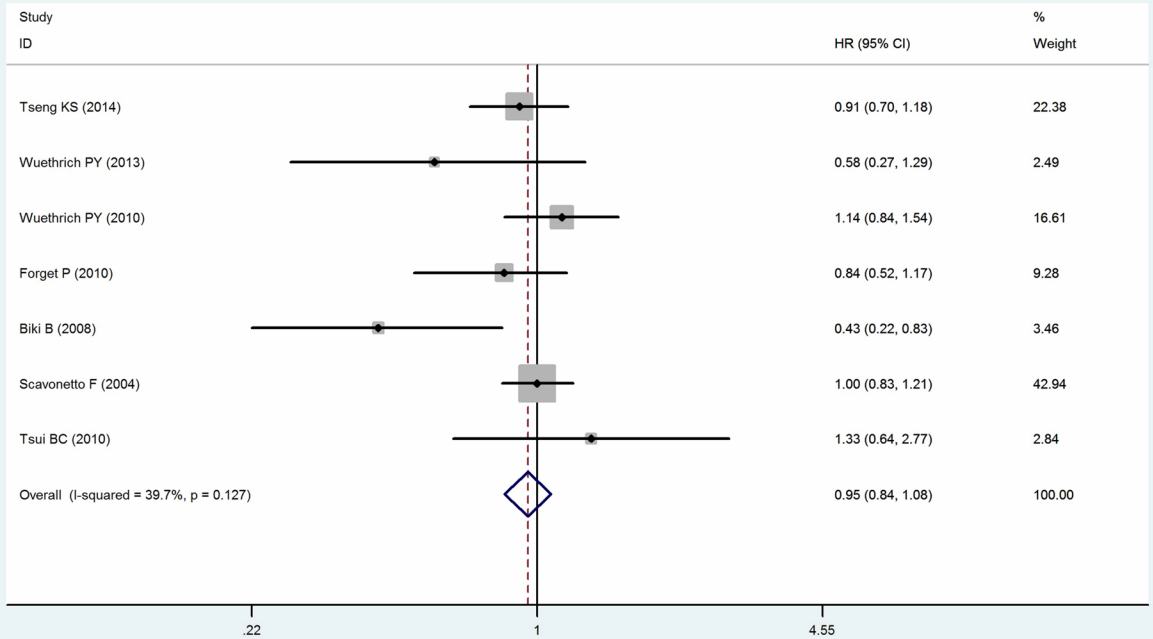

Figure 3. Forest plot for the meta-analysis of the association between neuraxial anesthesia with RFS with fixed-effects model. The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the squares reflects the weight. The diamond represents the summary HR and 95% CI. CI, confidence interval; HR, hazard ratio.

Table 2. Stratified analysis of neuraxial anesthesia and RFS

Variables	Group	Case/control	HR (95% CI)	I^2	P^h	*P*
	Overall (7)	3707/3385	0.95 (0.84-1.08)	39.7%	0.127	0.426
Design type	Retrospective (6)	3658/3335	0.94 (0.83-1.07)	45.2%	0.104	0.348
	Prospective (1)	49/50	1.33 (0.64-2.77)	/	/	/
Sample size	≥500 (3)	3386/2923	0.95 (0.82-1.10)	0.0%	0.690	0.493
	<500 (4)	321/462	0.81 (0.48-1.37)	67.4%	0.027	0.440
NOS	≥7 (5)	3556/3212	0.97 (0.85-1.10)	0.0%	0.486	0.633
	<7 (2)	151/173	0.75 (0.25-2.26)	80.0%	0.025	0.607

HR, hazard ratio; CI, confidence interval; P^h, *P*-value of heterogeneity test; NOS, The Newcastle-Ottawa Scale.

spective and 1 prospective studies were estimated. The sample sizes ranged from 148 to 3284. Meanwhile, 3 studies explore the association of neuraxial anesthesia with OS, while there are 7 studies to detect the association between neuraxial anesthesia and RFS. The relevant characteristics were shown in **Table 1**.

Quantitative synthesis

Meta-analysis for neuraxial anesthesia with OS: Only 3 studies explore the association of neuraxial anesthesia with OS. Apparent heterogeneity was found (I^2=59.5%, P^h=0.085), so random effects model was applied to calculate the combined HR and 95% CI. Consequently, the pooled data indicated there was no association between two paired groups in comparison with GA (HR=1.19, 95% CI=0.73-1.94, P=0.474) (**Figure 2**).

Meta-analysis for neuraxial anesthesia with RFS: There are 7 studies to detect the association between neuraxial anesthesia and RFS. No significant heterogeneity was found (I^2=39.7%, P^h=0.127), so fixed effects model was used to calculate the combined HR and 95% CI. As a result, the result suggested that there was no association between neuraxial anesthesia and RFS in comparison with GA (HR=0.95, 95% CI=0.84-1.08, P=0.426) (**Figure 3**). Additionally, no association was found in different subgroups of study design, sample size and NOS scores (**Table 2**).

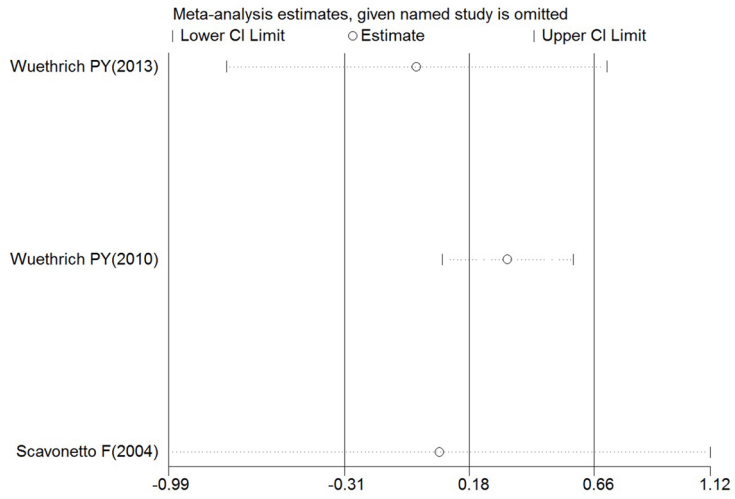

Figure 4. Sensitivity analysis of the neuraxial anesthesia with OS. The studies individually removed and the stable results were confirmed.

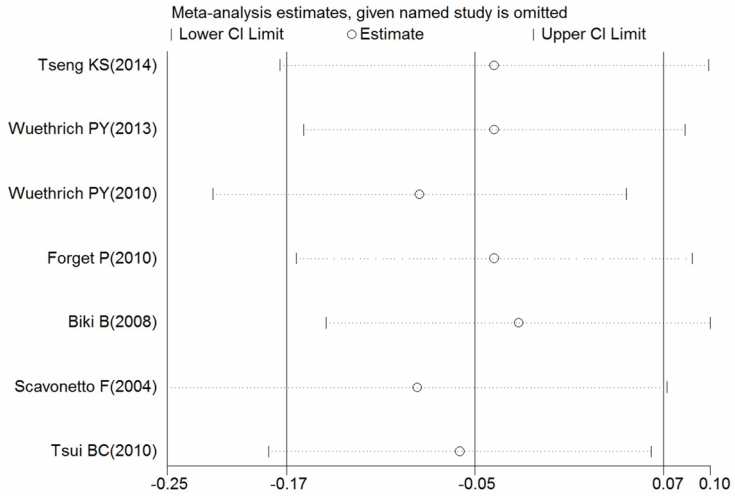

Figure 5. Sensitivity analysis of the neuraxial anesthesia with RFS. The studies individually removed and the stable results were confirmed.

Sensitivity analysis

Any single study here was deleted at a time to assess the specific effect of the individual data on the pooled HRs, and one-way sensitivity analysis suggested pooled results were relatively stable in OS (**Figure 4**) and RFS (**Figure 5**).

Publication bias evaluation

The funnel plot was used to evaluate publication bias. Egger's test and Begg's test indicated that publication bias was not found in OS (P=0.751 and P=1.00, respectively), and RFS (P=0.249 and P=0.368, respectively). Meanwhile, no publication bias was found in each subgroup of meta-analysis.

Discussion

In the present meta-analysis, our results indicated that there was no favorable correlation between neuraxial anesthesia and prognosis of prostate cancer patient after surgery. For RFS, the same results were detected in different subgroup analysis of study design, sample size and NOS scores. Our results from pooled meta-analysis are in coincidence with most, even not all, results from currently available literature.

Recently, the impact of neuraxial anesthesia on cancer recurrence and survival for patients is a new research hotspot. It may be involved in reducing immune cell functions including T cell, and NK cell, neutrophil cell, macrophage cell functions [22]. Privious study found that intraoperative use of epidural anesthesia was associated with increased free survival after surgery in different cancer patients. Cummings KC et al. [23] also found that epidural use is closely linked with improved survival in patients with nonmetastatic colorectal cancer after surgery while it does not support an association of epidural use with decreased cancer recurrence. Likewise, Exadaktylos AK et al. [24] detected that paravertebral anesthesia reduced the potential of cancer recurrence or metastasis for breast cancer surgery. Conversely, a few studies have indicated no significant effect of neuraxial anaesthesia on cancer recurrence and survival. Using neuraxial anaesthesia could not reduce the risk of tumour recurrence and mortality during brachytherapy for patients with cervical cancer compared with general anaesthesia by Ismail H et al. [25]. Apropos of prostate cancer, the impact of neuraxial anesthesia on cancer recurrence and survival for patients were controversial. So, we performed the cur-

rent meta-analysis for detecting the potential correlation between neuraxial anesthesia and cancer recurrence and survival in overall population and corresponding subgroups.

It is well known that host defense as the critical determinant of tumor progression is well-established, and the function of natural killer (NK) cells is the most essential ingredient in recognizing and killing tumor cells in host defense [26]. Recently, more attention has been paid to exploring various perioperative factors, which could shift the balance toward progression of minimal residual disease. Immune suppression may contribute to the expansion of minimal residual disease after surgical resection. Thus, minimal residual disease often results in local or metastatic recurrence under the circumstance of low host defense [27]. To date, the common perioperative factor is surgical stress, which surpresses cytotoxic T-cell and NK cell functions. It leads to imbalance of tumor-related antiangiogenic factors and proangiogenic factors [28]. Additionally, suppression of NK cell activity is closely linked with the invasiveness of the surgery, which often occurs during hours of surgery, even lasts a few days after surgery [29]. Another perioperative factor is opioids. Opioids inhibit both cellular and humoral immune function in humans, including antibody production, NK cell activity, cytokine secretion, lymphocyte proliferative responses to mitogens [30, 31]. Furthermore, recent research shows that morphine is proangiogenic and promotes breast tumor growth in rodents [32].

The mechanism of neuraxial anaesthesia on cancer recurrence or survival for patients remains unclear. The significant impact of administration of neuraxial anesthesia on cancer recurrence and survival may be explained by immunosuppression during surgery, or in the postoperative period. It has been illustrated to suppress immune functions of NK and T cells for several days [30]. Moreover, epidural anesthesia shifted the Th1/Th2 balance towards Th1, which destroyed tumor microenvironment [28]. Additionally, neuraxial anesthesia can attenuate neuroendocrine stress by cutting off neural transmission and blocking decreasing activation of the sympathetic nervous system. Neuroendocrine stress may bring about immunosuppression during surgery [33, 34]. Subsequently, neuraxial anesthesia affects immunosuppression. Therefore, administration of neuraxial anesthesia may bring about better results regarding cancer recurrence and survival. However, our meta-analysis failed to find an association between neuraxial anesthesia and prognosis of prostate cancer patient after surgery, which results could be explained by the relatively small retrospective analyses, lacking sufficient power to identify potentially treatment effects.

Actually, our meta-analysis has its limitations. Firstly, it is subjected to recall or selection bias of retrospective study. Secondly, only published studies could not provide sufficient evidences in this meta-analysis. Finally, our conclusion was checked by crude estimation rather than adjusted data. Therefore, other risk factors such as environmental effects and genetic factors should also be taken into consideration in advanced research. Meanwhile, the heterogeneity suggested there are potential or undiscovered factors in included publications. Detailed prospective studies comprising large cohort size are required to confirm our conclusions.

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Disclosure of conflict of interest

None.

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