BIOCHEMICAL RECURRENCE RISK IN PROSTATE CANCER PATIENTS WITH PERINEURAL INVASION: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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STATEMENT BY AUTHOR

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APPROVAL BY THESIS DIRECTOR

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Thesis Director

03/29/2018

Defense Date

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Abstract

Background: The association between PNI observed in radical prostatectomy (RP) and the risk of BCR in patients with prostate cancer remains unclear. We performed a systematic review and meta-analysis to quantify overall BCR risk in subgroups of individuals with PNI that underwent RP for localized prostate cancer.

Methods: Eligible studies were retrieved from PubMed, Embase, Web of SCIENCE, Scopus and Google Scholar. Pooled multivariate hazard ratios (MHR), univariate hazard ratios (UHR) and univariate odds ratios (UOR) were calculated for eligible studies. Sub-analyses were performed for studies with mean follow-up time (MFU) of less than 2 years (y), 2-3 y and more than 3 y. Analyses were performed using random effect (RE) models to assess the pooled relative effects under consideration of heterogeneity among included studies.

Results: A total of 28 studies were retained. The MHR analysis (n=22) indicated that PNI is significantly associated with BCR events (HR=1.53, 95%CI=1.33-1.78, p<0.0001). MHR sub-analysis revealed that the PNI~BCR association was not significant for studies with MFU less than 2 y (HR=1.39, 95%CI=0.92-2.08, p=0.115), but was for 2-3 y (HR=2.01, 95%CI=1.48-2.72, p<0.0001) and more than 3 y (HR=1.48, 95%CI=1.25-1.75, p<0.0001). The UHR analysis for 16 studies showed that PNI is significantly associated with BCR events (HR=1.94, 95%CI=1.46-2.57, p<0.0001). UHR sub-analysis revealed that the PNI~BCR association was not significant for studies with MFU 2-3 y (HR=1.35, 95%CI=0.48-3.85, p=0.572), but was for less than 2 y (HR=1.78, 95%CI=1.06-2.99, p=0.028) and more than 3 yr (HR=2.09, 95%CI=1.69-2.58, p<0.0001). The UOR analysis for 3 studies showed that PNI is significantly associated with BCR events (OR=1.59, 95%CI=1.19-2.11, p=0.002). UOR sub-analysis revealed that the PNI~BCR association was significant for studies with MFU 2-3 y (OR=7.59, 95%CI=2.66-21.70, p<0.0001) and more than 3 y (OR=3.70, 95%CI=2.27-6.04, p<0.0001).

Conclusions: Although individual studies differed in their findings about the association between PNI and predicted BCR risk, our meta-analyses revealed a significant association between PNI and predicted BCR risk in studies with longer follow-up. This suggests that BCR, if it were to occur, is likely to be detectable 2-3 y post-surgery. Thus, there is an increased risk of BCR in pts with PNI; if expressed, this risk is to show anytime 2-3 y post-surgery.

Student's contributions: Stephanie Fletcher, the student, performed all statistical analyses, drafted the initial manuscript and was involved with all steps of this thesis. Dr. Abraham supervised all steps of this meta-analysis. Jennifer Martin assisted with part of the database searches and critically reviewed the manuscript. Dr. McBride, Dr. Abraham and Dr. Gomez critically reviewed the manuscript. Dr. Abraham and Stephanie Fletcher critically reviewed the statistical analyses and revised the manuscripts after critical review.

Introduction

Prostate cancer is a disease that plagues approximately 11.6 % of men, at some point during their lifetime [1]. In 2014, there was an estimated 3.1 million men living with prostate cancer in the United States alone [1]. However, despite the prevalence of this disease, prostate cancer has a 98.6% relative survival rate, given that 79.2 % of patients with prostate cancer are diagnosed at the local stage [1]. Yet, as survival rates are based on large populations, they are unable to predict or quantify the likelihood of biochemical recurrence [1].

Prostate cancer is highly manageable, if detected at the local disease stage. There are many treatment options for management of prostate cancer including watchful waiting, surgery, radiation therapy, hormone therapy, chemotherapy, biologic therapy and bisphosphonate therapy [1]. As an estimated number of 79.2 % of detected disease is localized, radical prostatectomy (RP) is the procedure of choice for treatment of localized prostate cancer [2]. During this procedure, the prostate is removed as well as surrounding tissues, seminal vesicles, and on a case-by-case basis, removal of surrounding lymph nodes [1].

Perineural invasion (PNI) found during a microscopic analysis of RP specimens from patients with prostate cancer is often indicative of metastasis [3]. It is unclear whether or not PNI presence during examination of RP specimens can predict future risk of biochemical recurrence (BCR), which is the state of an increasing prostate-specific antigen (PSA) level, often used as a predictor for the

development of distant metastases [4]. As PNI and BCR are related to one another, understanding how the significance of observed PNI can be an indicative predictor of BCR risk is important to be able to understand to improve the maintenance of the disease. However, the association between PNI observed in radical prostatectomy and the risk of BCR in patients with prostate cancer remains unclear. A systematic review and meta-analysis was performed to quantify the overall BCR risk in subgroups of individuals with PNI that underwent RP for localized prostate cancer.

Literature Review

Retrospective analysis studies and randomized controlled trials of patients with prostate cancer typically assess the overall survival and risk of metastasis of patients receiving various treatment options. Several retrospective analysis studies and randomized controlled trials have been performed to evaluate whether or not PNI is a significant predictor of BCR. However, results have been varied, and as such, a systematic review and meta-analysis is needed to quantify the overall BCR risk in subgroups of individuals with PNI that underwent RP for localized prostate cancer.

Up to date, RP is a treatment option for patients with localized prostate cancer. RP has proven to be highly effective when performed as an initial therapy, and as such, is a good treatment option for patients that are good candidates for the procedure [5]. When RP was compared to watchful waiting in a randomized

clinical trial of 695 patients with localized disease, it was noted that patients that received RP had significant improvements in overall survival, disease-specific survival and risk of metastasis and local progression [5].

In a systematic review published in 2007, Harden et al. evaluated the impact of PNI in biopsies on BCR risk of patients with prostate cancer [6]. The authors found that PNI was a predictor of BCR, and that interventional treatment could yield better outcomes for patients with localized disease but did not base these claims on strong statistical evidence [6].

In 2015, a meta-analysis was performed by Meng et al., that evaluated whether or not PNI was an independent predictor of BCR of prostate cancer after local treatment [7]. This study included only 12 studies in their meta-analysis, 6 of which were studies evaluating the presence of PNI in RP specimens [7]. The authors found that overall, PNI was associated with a 1.6-fold higher risk of BCR after local treatment [7]. They also conducted sub-analyses to determine the association according to primary treatment modalities and found that PNI was a significant predictor of BCR in RP specimens [7]. However, this study had both a limited study population (6 studies) for evaluation of PNI as a significant predictor of BCR in RP specimens as well as a generalized focus on local therapies overall and did not analyze large-scale therapy-specific risk.

In another systematic review and meta-analysis by Raymond et al. that was published in 2017 [8], efficacy of various prognostic tools and their relation to

clinical outcomes following radiation therapy was evaluated. In this study, a majority of papers included attempted to predict biochemical recurrence risk, however the main focus of this study was to evaluate how tools can aid decision making in developing more accurate predictions of clinical outcomes and did not indicate any importance of noting PNI presence during treatment [8].

Our meta-analysis expands upon the findings of prior studies by evaluating the association between PNI noted during RP and predicted BCR risk for patients with prostate cancer. Further, our meta-analysis analyzes mean follow-up time to determine the optimal follow-up period during which, if BCR were to occur, it could be detectable, to aid in the maintenance of the disease.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).

Search Strategy and Data Extraction

The appropriate search strategy was formulated with the help of an independent librarian (Supplementary Materials A). Two authors independently searched PubMed, Embase, Web of SCIENCE, Scopus and Google Scholar databases, involving studies without date restrictions through February 13, 2018 using a standard Excel form for data extraction. Languages of screened studies were

limited to studies that were published in English. The references of included studies were cross-checked to identify any additional studies for inclusion. The results of this initial screening were compared between the two authors results and any discrepancies between the authors were resolved through discussion. Results were only included for studies that reported the significance of PNI as a predictor of BCR.

Study Selection

Clinical trials of patients diagnosed with prostate cancer who were treated with RP and which evaluated the significance of PNI as a predictor of BCR were identified and included. 3 studies were included that were only published as abstracts only. Studies were excluded that did not provide data on PNI or number of BCR events; studies that were not readily available in English; and studies that did not perform multivariate or univariate analyses on PNI presence.

Data Synthesis and Analysis

The primary outcome was the significance of PNI as a predictor of BCR. Eligible studies were retrieved from PubMed, Embase, Web of SCIENCE, Scopus and Google Scholar. Pooled multivariate hazard ratios (MHR), univariate hazard ratios (UHR) and univariate odds ratios (UOR) were calculated for eligible studies. Sub-analyses were performed for studies with mean follow-up time of less than 2 years, 2-3 years and more than 3 years. Analyses were performed

using random effect (RE) models with 95% confidence intervals (CIs) to assess the pooled relative effects under consideration of heterogeneity among included studies. Heterogeneity (I^2) was assessed by using a Cochran's chi-squared test and were depicted through Forrest plots for all analyses and sub-analyses. For results that displayed high levels of heterogeneity, suspicious studies were removed, after which the analysis was re-run and corresponding results analyzed to ensure that outlying studies did not bias the results. All analyses were performed using STATA Data Analysis and Statistical Software Version 15 software (College Station, Texas, USA).

Results

Search Results

The initial literature search identified a total of 202 studies (PubMed 14; Embase 146; Web of SCIENCE 28; Scopus 11; and Google Scholar 3). A total of 32 duplicates were removed (Figure 1). A total of 170 studies were screened for eligibility after assessment by title and abstract (Figure 1). 116 studies were excluded that did not match the inclusion criteria (Figure 1). A total of 54 studies were secondarily assessed for eligibility, resulting in 28 studies that met inclusion criteria and were included in the final qualitative and quantitative synthesis (Figure 1). The year of publication, country of publication, mean follow-up time, number of BCR events, number of patients with PNI, mean population age, total

number of patients, univariate hazard ratios with 95% CIs, multivariate hazard ratios with 95% CIs, univariate odds ratios with 95% CIs, and their respective p-values were collected for each study (Table 1).

Study Characteristics

The characteristic of the 28 included studies are summarized in Table 1. They were conducted between 2005 and 2017. 22 studies were retrospective analysis studies (RAs) [9-30]; 5 studies were randomized controlled studies (RCTs) [31-35]; and 1 study was a test-tube lab research study [36]. 11 studies were conducted in the United States [12-14, 20, 22-23, 25-26, 28, 30-31]; 4 studies were conducted in South Korea [17-19, 21]; 4 studies were conducted in Japan [16, 32-33, 35]; 2 studies were conducted in Belgium [10, 34]; 1 study was conducted in Norway [9]; 1 study was conducted in Russia [11]; 1 study was conducted in Spain [15]; 1 study was conducted in Brazil [36]; 1 study was conducted in the Netherlands [29]; 1 study was conducted in China [27]; and 1 study was conducted in Australia [24]. All 28 studies were published in English, and one study was excluded due to language (language) [37].

Outcomes:

The significance of PNI as a predictor of BCR was evaluated in all 28 studies. 27 studies reported the number of BCR events noted and 27 studies reported the number of patients with PNI [Table 1]. The one study that did not report the

number of BCR events noted was a published ASCO 2017 abstract, and thus the full version of the study was not yet available [27]. The one study that did not report a specific number of patients with PNI correlated Gleason score with PNI presence [28]. Our meta-analysis sought to determine whether PNI is a predictor of BCR in patients that received RP as treatment for prostate cancer as present study results are very mixed. PNI was found to be a significant predictor of BCR in 20 studies [11, 13-17, 19, 22-23, 25-28, 30-36]. PNI was found to not be a significant predictor of BCR in 8 studies [9-10, 12, 18, 20-21, 24, 29]. 22 studies provided multivariate hazard ratios with 95% CIs. The multivariate hazard ratios analysis (n=22) indicated that PNI is significantly associated with BCR events (HR=1.53, 95%CI=1.33-1.78, p<0.0001) [Figure 2-3, Table 2-3]. This analysis was performed both with and without Ost et al. [34], a study with outlying CIs, to ensure that the study did not affect the overall results [Figure 2-3, Table 2-3]. A multivariate hazard ratios sub-analysis revealed that the PNI~BCR association was not significant for studies with mean follow-up time less than 2 years (HR=1.39, 95%CI=0.92-2.08, p=0.115) [Supplementary Figure 1a], but was for 2-3 years (HR=2.01, 95%CI=1.48-2.72, p<0.0001) [Supplementary Figure 1b] and more than 3 years (HR=1.48, 95%CI=1.25-1.75, p<0.0001) [Supplementary Figure 1c]. The univariate hazard ratios analysis for 16 studies showed that PNI is significantly associated with BCR events (HR=1.94, 95%CI=1.46-2.57, p<0.0001) [Figure 4-5, Table 4-5]. This analysis was performed both with and without Chernyaev et al. [11], a study with outlying CIs, to ensure that the study did not

affect the overall results [Figure 4-5, Table 4-5]. Univariate hazard ratios sub-analysis revealed that the PNI~BCR association was not significant for studies with mean follow-up time 2-3 years (HR=1.35, 95%CI=0.48-3.85, p=0.572) [Supplementary Figure 2b], but was for less than 2 years (HR=1.78, 95%CI=1.06-2.99, p=0.028) [Supplementary Figure 2a] and more than 3 years (HR=2.09, 95%CI=1.69-2.58, p<0.0001) [Supplementary Figure 2c]. The univariate odds ratios analysis for 3 studies showed that PNI is significantly associated with BCR events (OR=1.59, 95%CI=1.19-2.11, p=0.002) [Figure 6-7, Table 6-7]. This analysis was performed both with and without Rishtau et al. [25], a study with outlying CIs, to ensure that the study did not affect the overall results [Figure 6-7, Table 6-7]. Univariate odds ratios sub-analysis revealed that the PNI~BCR association was significant for studies with mean follow-up 2-3 years (OR=7.59, 95%CI=2.66-21.70, p<0.0001) [Supplementary Figure 3a] and more than 3 years (OR=3.70, 95%CI=2.27-6.04, p<0.0001) [Supplementary Figure 3b].

Discussion:

Despite the prevalence of prostate cancer, there has been disagreement in terms of the prognostic value of PNI in predicted BCR risk for individuals that underwent RP for prostate cancer treatment. Additionally, individual studies differed in their findings about the association between PNI and predicted BCR risk. Thus, our meta-analyses revealed a significant association between PNI and

predicted BCR risk for prostate cancer patients that had RP in studies with longer follow-up.

Performing sub-analyses helped to assess the importance of follow-up time post-radical prostatectomy in regard to eliminating risk of BCR in patients with PNI. These findings suggest that BCR, if it were to occur, is likely to be detectable 2-3 years post-surgery. As such, it was found that there is an increased risk of BCR in patients with PNI; and if expressed, this risk is to show anytime 2-3 years post-surgery.

This was the first systematic review and meta-analysis to focus on the associated between PNI and BCR in patients that received RP treatment for localized prostate cancer as well as assess the most effective follow-up period in order to reduce BCR risk. Given PRISMA guidelines and the large number of studies included in this analysis, our study provided adequate evidence for the positive association between PNI and BCR in prostate cancer patients that had RP as main-line treatment. Additionally, when removing the studies with the most weight: Ost et al. [34] for the multivariate hazard ratios analysis; Chernyaev et al. [11] for the univariate hazard ratios analysis; and Rishtau et al. [25] for the univariate odds ratios analysis, the pooled result remained consistent.

However, it is important to note that there were some limitations in our study that could have affected our results. First, the analyses were performed by STATA software, rather than the standard Comprehensive Meta-Analysis (CMA)

software because the platform of CMA did not meet our need for the limited data we collected on a standard Excel sheet. Also, there were a handful of studies that were excluded from our analysis because they either did not report efficacy measures (i.e. odds ratios, hazard ratios or risk difference) or they did not report a clear number of patients in each arm. Additionally, for those studies that reported odds ratios only, we ran separate analyses from those that reported hazard ratios. Lastly, the results in our analyses (odds ratios and hazard ratios) display a high level of heterogeneity. However, we sought to exclude the suspicious studies that we thought could have contributed to the high level of heterogeneity, repeated the analyses, and analyzed the results, the results still yielded a high level of heterogeneity- illustrating the need for this meta-analysis.

Appendix A: Figures and Tables

Figure 1. Flow diagram of the study selection process

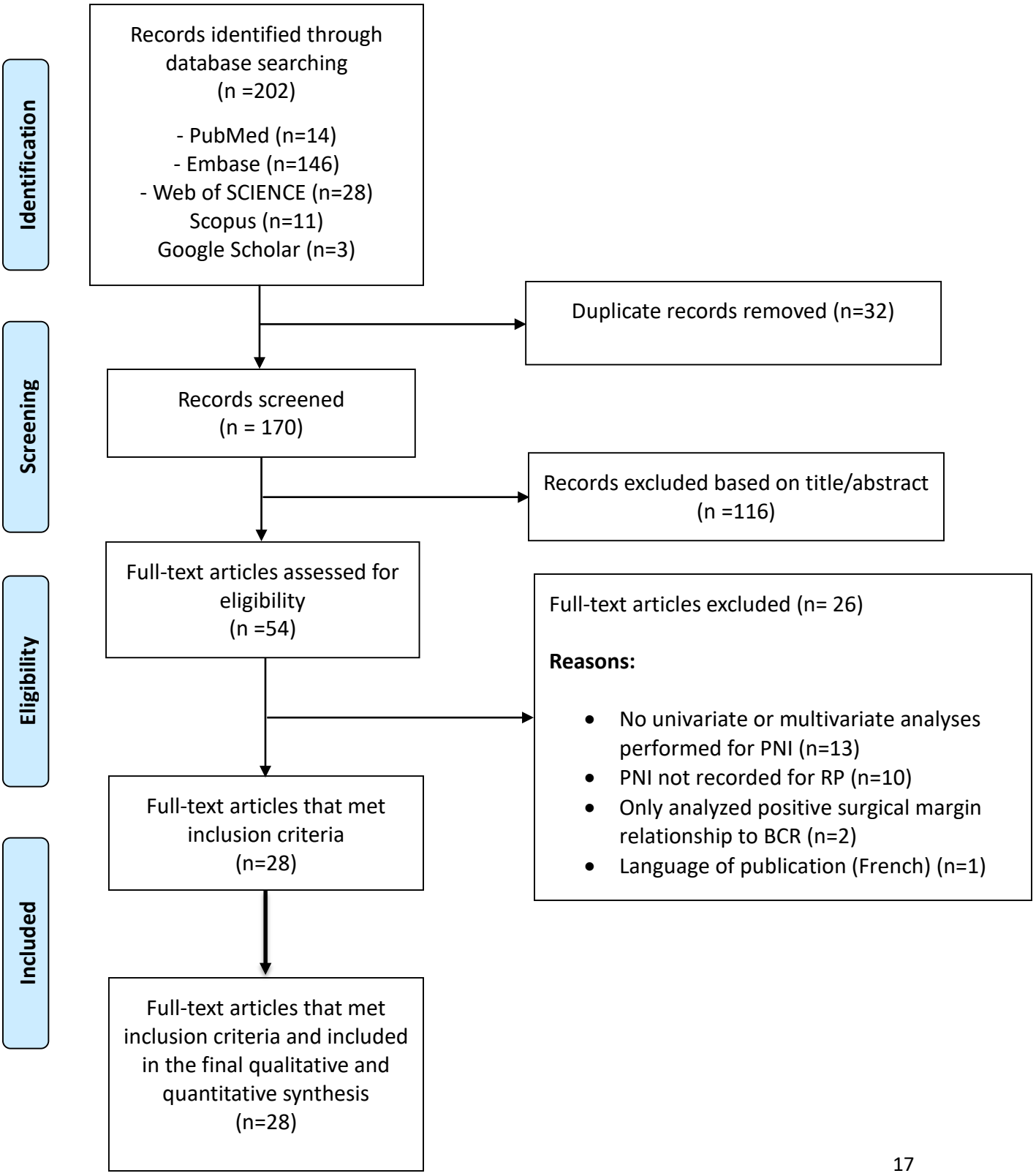
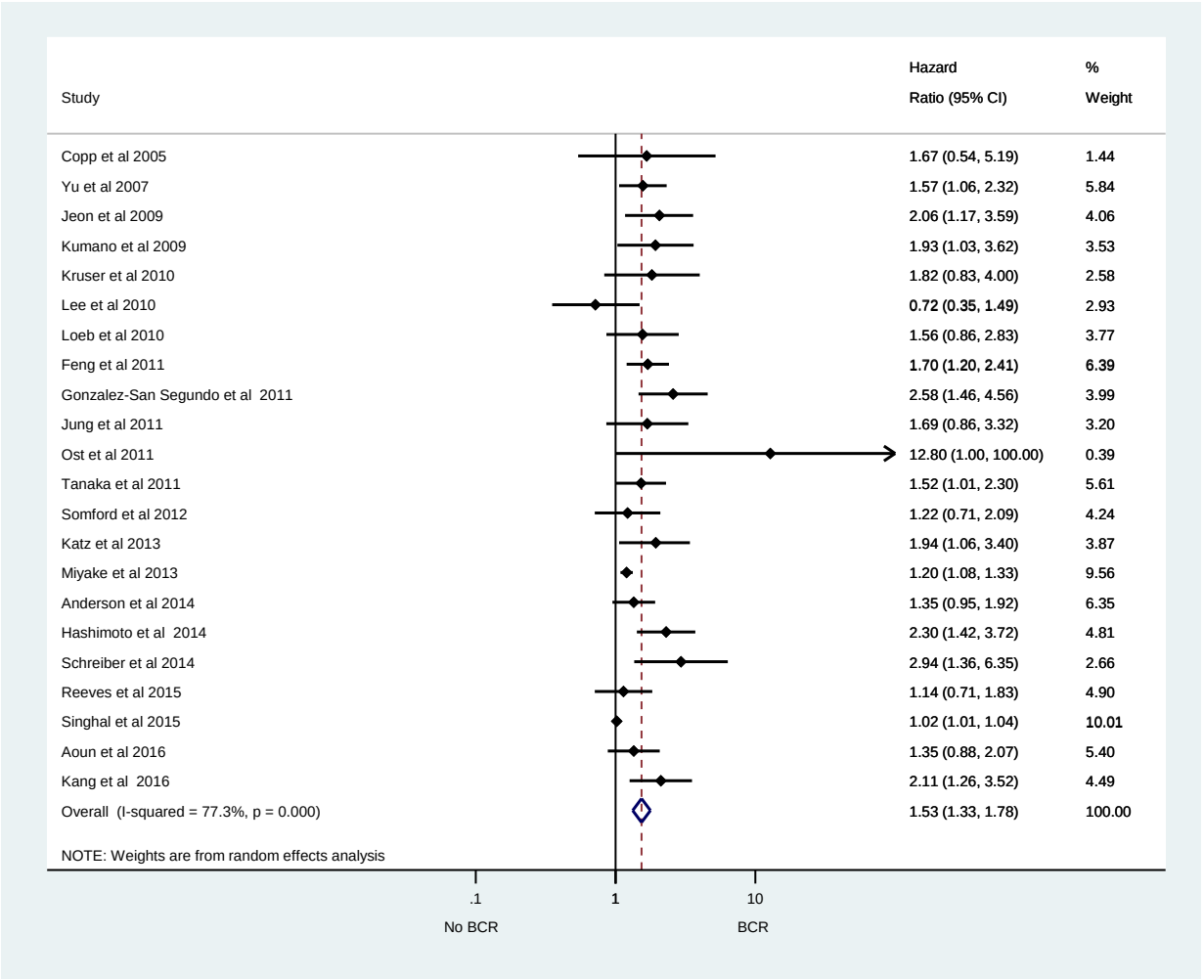


Table 1. Characteristics of Included Studies

Author	Year	Country	Median follow-up time (mo.)	Number of BCR events	Patients with PNI	Median population age (yrs)	Number of patients total	Univar, 95% CI	p-values	Multivar, 95% CI	p-values
Anderson et al.	2014	Norway	89	170 (31.8%)	535 (100%)	62	535	---	---	HR 1.35 (0.95-1.92)	---
Aoun et al.	2016	Belgium	108	107 (11.7%)	305 (33.5%)	64	910	HR 1.29 (0.87-1.9)	p=0.2	HR 1.35 (0.88-2.07)	p=0.17
Bittner et al.	2010	**United States**	7.1	71 (4.4%)	486 (30.1%)	66	1613	HR 1.78 (1.35-2.36)	p=0.021	--	p=0.491
Chernyaev et al.	2013	Russia	30.5	64 (16.6%)	188 (48.7%)	61	386	HR 0.42 (0.181–0.955)	p=0.039	---	---
Copp et al.	2005	United States	45	73 (79%)	17 (18.7%)	69.1	93	---	---	HR 1.67 (0.54-5.19)	p= 0.37
Feng et al.	2011	United States	62.2	416 (64%)	220 (33.8%)	69.4	651	---	---	HR 1.7 (1.20-2.41)	p<0.006
Godoy et al	2009	United States	33.5	646 (49.4%)	191 (14.6%)	58.42	1308	OR 2.79 (1.824–4.269)	p<0.001	OR 2.03 (1.234–3.331)	p=0.005
Gonzalez-San Segundo et al.	2011	Spain	28	83 (30.6%)	25 (9.2%)	63.5	271	---	p=0.00	HR 2.58 (1.46–4.56)	p=0.001
Hashimoto et al.	2014	Japan	10.8	80 (10.2%)	557 (71.1%)	64.3	784	---	p<0.0001	HR 2.30 (1.42-3.72)	p=0.0007
Jeon et al.	2009	South Korea	21.8	67 (28.3%)	100 (42.5%)	64.5	237	HR 2.68 (1.64–4.38)	p<0.001	HR 2.06 (1.17–3.59)	p=0.011
Jung et al.	2011	South Korea	18.43	45 (11.1%)	170 (41.8%)	63.24	407	HR 2.949 (1.597–5.445)	p=0.001	HR 1.688 (0.859–3.317)	p=0.129
Kang et al.	2016	South Korea	48	300 (14.7%)	1410 (69.3%)	67	2034	HR 2.92 (2.16–3.94)	p<0.001	HR 2.11 (1.26–3.52)	p=0.004
Katz et al.	2013	Brazil	51.40	56 (9.35%)	105 (17.5%)	61	599	HR 1.940 (1.106, 3.403)	---	HR 1.940 (1.106,3.403)	p=0.0003
Kruser et al.	2010	United States	32.4	30 (27.8%)	43 (39.8%)	63	108	HR 1.97 (0.96-4.06)	p=0.066	HR 1.82 (0.83-4)	p=0.14
Kumano et al.	2009	Japan	3	10 (3.74%)	37 (13.85%)	69.7	267	HR 2.45 (1.46-4.11)	p=0.039	HR 1.93 (1.03-3.62)	p=0.14
Lee et al.	2010	South Korea	42.4	83 (23.0%)	188 (52.1%)	69	361	---	p=0.018	HR 0.718 (0.352-1.468)	p=0.364
Loeb et al.	2010	United States	34	57 (4.5%)	188 (15.0%)	56	1256	---	---	HR 1.56 (0.86-2.83)	p< 0.001
Miyake et al.	2013	Japan	48.9	211 (22.0%)	661 (68.9%)	67.5	959	HR 1.97 (1.64-2.37)	p<0.001	HR 1.2 (1.08-1.33)	p=0.34
Ost et al.	2011	Belgium	36	16 (9.0%)	66 (37.1%)	63.5	178	---	---	HR 12.8 (1.6-100.0)	p < 0.05
Pierorazio et al.	2013	United States	120	637 (54.3%)	240 (20.5%)	60.5	1173	OR 2.51 (1.83–3.4)	p<0.001	OR 4.71 (1.10–20.2)	p=0.04
Reeves et al.	2015	Australia	8	238 (15.9%)	1173 (78.35%)	62	1497	HR 2.30 (1.50–3.55)	p<0.0005	HR 1.14 (0.71-1.83)	p=0.602
Rishtau et al.	2015	United States	55.6	276 (11.04%)	454 (18.16%)	60	2500	OR 1.3 (0.92–1.9)	p=0.1348	---	---
Schreiber et al.	2014	United States	42	33 (16.3%)	37 (18.2%)	70	203	HR 2.99 (1.41-6.35)	p=0.01	HR 2.94 (1.36-6.35)	p=0.01
Shen et al.	2017	China	45	---	123 (46.4%)	---	265	HR 3.87 (1.66-9.01)	p=0.002	---	---
Singhal et al.	2015	United States	2.5	511 (12.15%)	---	61	4207	HR 1.01 (1.00 - 1.03)	p=0.06	HR 1.02(1.01 - 1.04)	p=0.002
Somford et al.	2012	Netherlands	40	102 (10.1%)	378 (27.1%)	63.8	1009	HR 2.20 (1.40–3.44)	p> 0.05	HR 1.22 (0.71–2.09)	p> 0.05
Tanaka et al.	2011	Japan	53	171 (36.5%)	226 (48.3%)	67.5	468	---	---	HR 1.523 (1.010–2.296)	p=0.045
Yu et al.	2007	United States	68	45 (7.68%)	112 (19.1%)	68	586	HR 1.71 (1.19 to 2.46)	p=0.004	HR 1.57 (1.06 to 2.32)	p=0.025

Figure 2. Forest plot showing the multivariate HR (including Ost et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

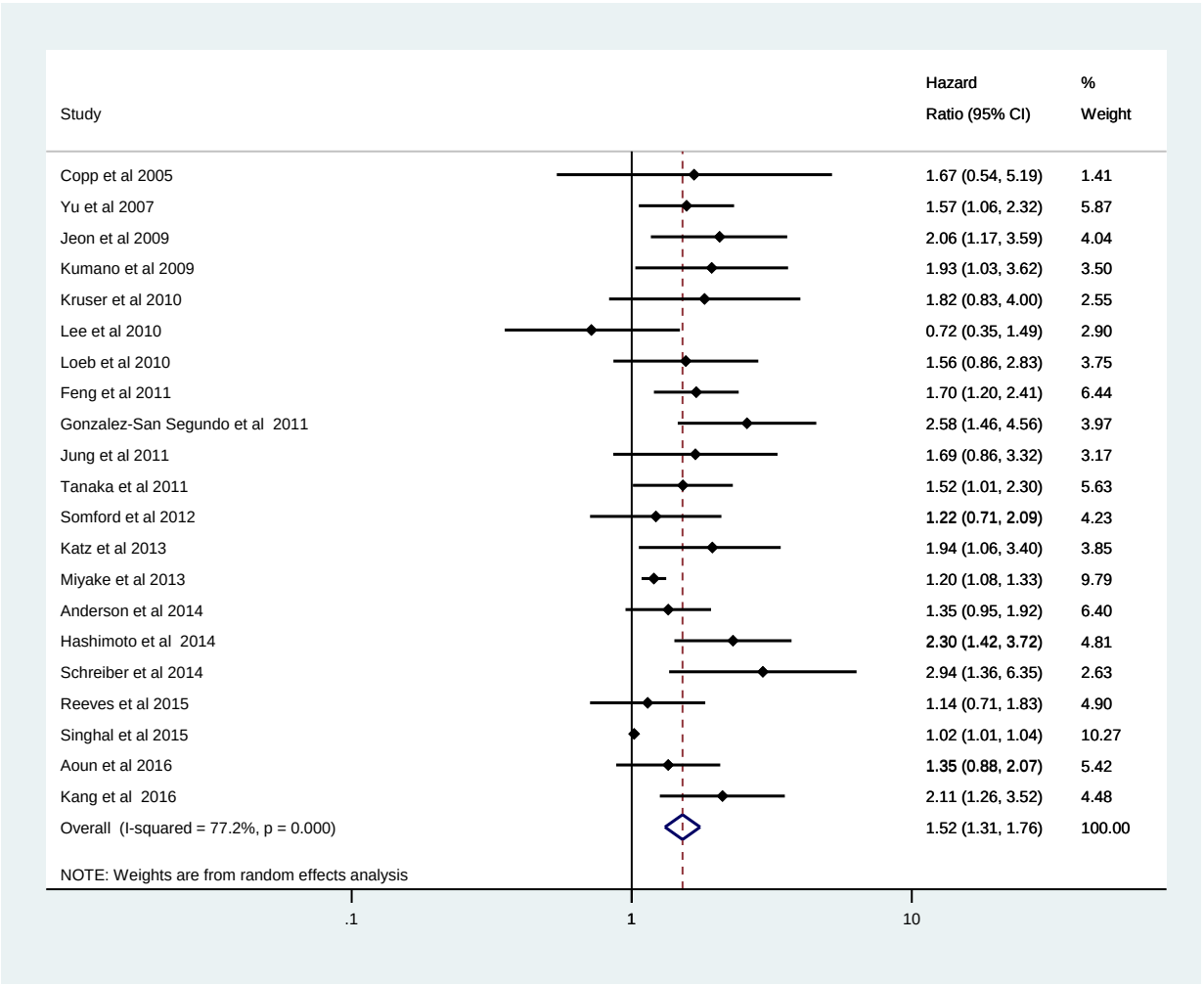
Table 2. Multivariate HR (including Ost et al.)

Study	ES	[95% Conf.	Interval]	% Weight
Copp et al 2005	1.670	0.540	5.190	1.44
Yu et al 2007	1.570	1.060	2.320	5.84
Jeon et al 2009	2.060	1.170	3.590	4.06
Kumano et al 2009	1.930	1.030	3.616	3.53
Kruser et al 2010	1.820	0.830	4.000	2.58
Lee et al 2010	0.718	0.352	1.486	2.93
Loeb et al 2010	1.560	0.860	2.830	3.77
Feng et al 2011	1.700	1.200	2.410	6.39
Gonzalez-San Segundo	2.580	1.460	4.560	3.99
Jung et al 2011	1.688	0.859	3.317	3.20
Ost et al 2011	12.800	1.000	100.000	0.39
Tanaka et al 2011	1.523	1.010	2.296	5.61
Somford et al 2012	1.220	0.710	2.090	4.24
Katz et al 2013	1.940	1.060	3.403	3.87
Miyake et al 2013	1.200	1.084	1.328	9.56
Anderson et al 2014	1.350	0.950	1.920	6.35
Hashimoto et al 201	2.300	1.420	3.720	4.81
Schreiber et al 2014	2.940	1.360	6.350	2.66
Reeves et al 2015	1.140	0.710	1.830	4.90
Singhal et al 2015	1.020	1.010	1.040	10.01
Aoun et al 2016	1.350	0.880	2.070	5.40
Kang et al 2016	2.110	1.260	3.520	4.49
D+L pooled ES	1.534	1.325	1.776	100.00

Heterogeneity chi-squared = 92.41 (d.f. = 21) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 77.3%
Estimate of between-study variance Tau-squared = 0.0557

Test of ES=1 : z= 5.73 p = 0.000

Figure 3. Forest plot showing the multivariate HR (excluding Ost et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Table 3. Multivariate HR (excluding Ost et al.)

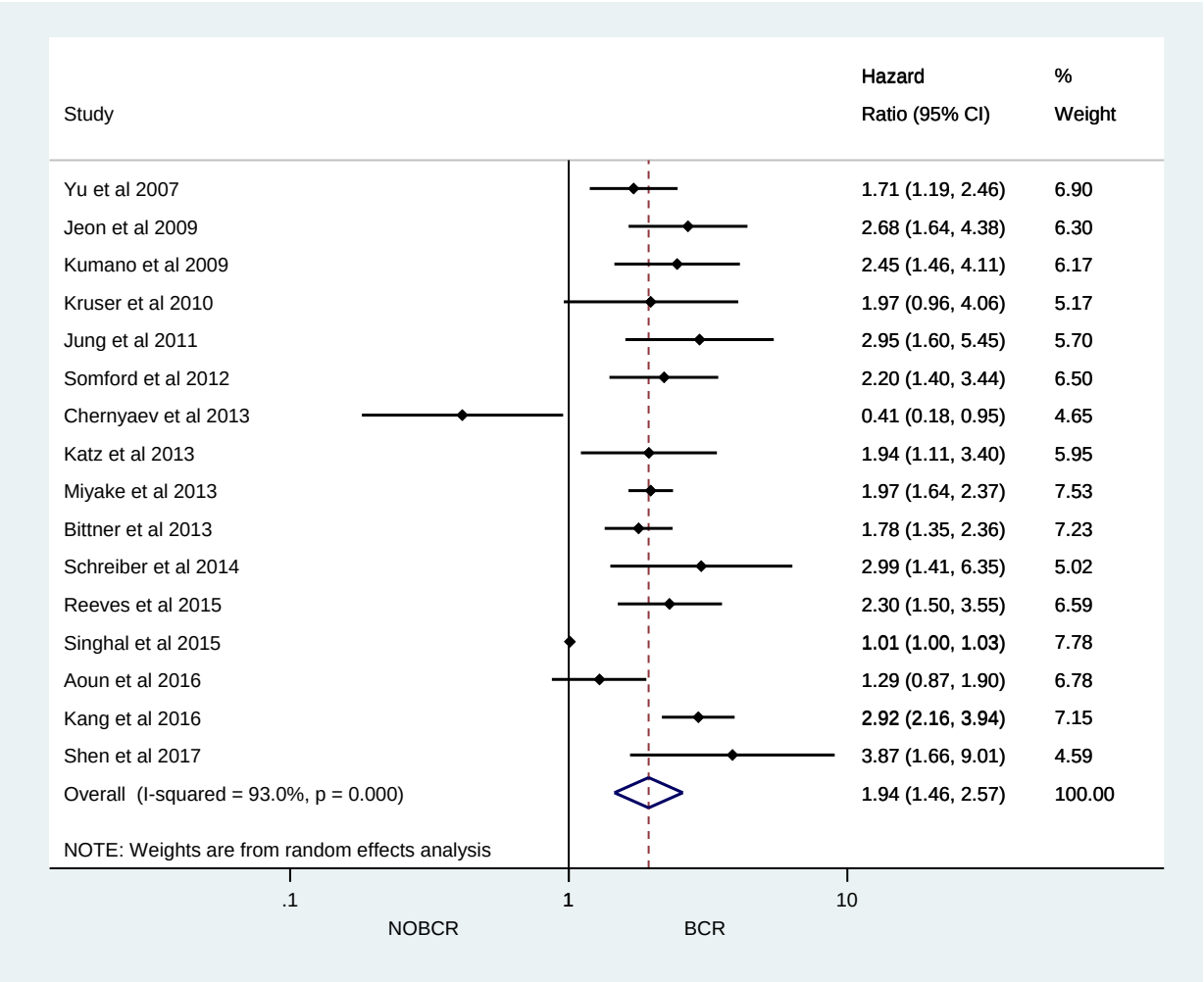
Study	ES	[95% Conf.	Interval]	% Weight
Copp et al 2005	1.670	0.540	5.190	1.41
Yu et al 2007	1.570	1.060	2.320	5.87
Jeon et al 2009	2.060	1.170	3.590	4.04
Kumano et al 2009	1.930	1.030	3.616	3.50
Kruser et al 2010	1.820	0.830	4.000	2.55
Lee et al 2010	0.718	0.352	1.486	2.90
Loeb et al 2010	1.560	0.860	2.830	3.75
Feng et al 2011	1.700	1.200	2.410	6.44
Gonzalez-San Segundo	2.580	1.460	4.560	3.97
Jung et al 2011	1.688	0.859	3.317	3.17
Tanaka et al 2011	1.523	1.010	2.296	5.63
Somford et al 2012	1.220	0.710	2.090	4.23
Katz et al 2013	1.940	1.060	3.403	3.85
Miyake et al 2013	1.200	1.084	1.328	9.79
Anderson et al 2014	1.350	0.950	1.920	6.40
Hashimoto et al 201	2.300	1.420	3.720	4.81
Schreiber et al 2014	2.940	1.360	6.350	2.63
Reeves et al 2015	1.140	0.710	1.830	4.90
Singhal et al 2015	1.020	1.010	1.040	10.27
Aoun et al 2016	1.350	0.880	2.070	5.42
Kang et al 2016	2.110	1.260	3.520	4.48
D+L pooled ES	1.519	1.314	1.755	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 87.81 (d.f. = 20) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 77.2%
Estimate of between-study variance Tau-squared = 0.0530

Test of ES=1 : z= 5.66 p = 0.000

Figure 4. Forest plot showing the univariate HR (including Chernyaev et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Table 4. Univariate HR (including Chernyaev et al.)

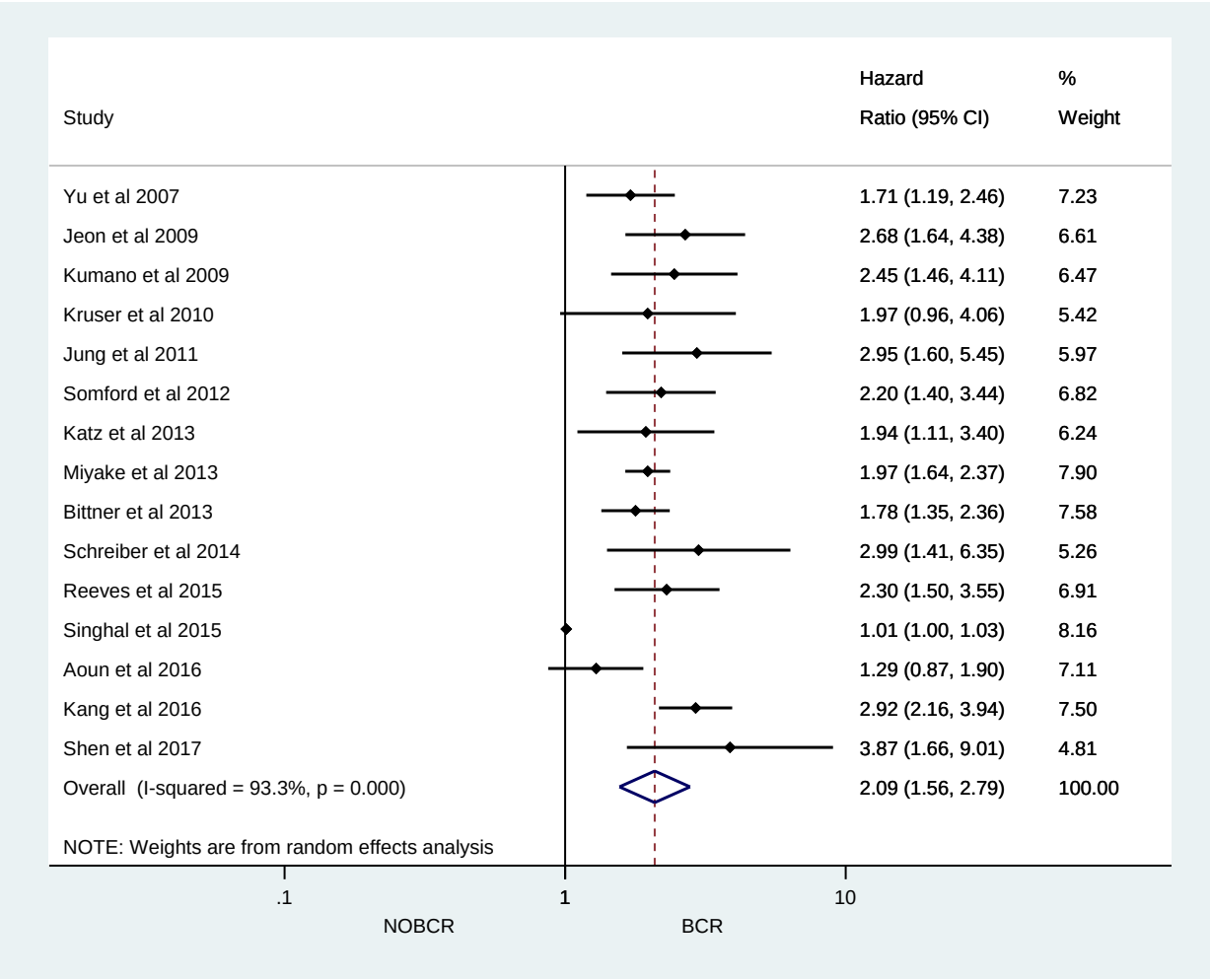
Study	ES	[95% Conf.	Interval]	% Weight
Yu et al 2007	1.710	1.190	2.460	6.90
Jeon et al 2009	2.680	1.640	4.380	6.30
Kumano et al 2009	2.450	1.459	4.115	6.17
Kruser et al 2010	1.970	0.960	4.060	5.17
Jung et al 2011	2.949	1.597	5.445	5.70
Somford et al 2012	2.200	1.400	3.440	6.50
Chernyaev et al 2013	0.415	0.181	0.955	4.65
Katz et al 2013	1.940	1.106	3.403	5.95
Miyake et al 2013	1.970	1.638	2.369	7.53
Bittner et al 2013	1.782	1.346	2.360	7.23
Schreiber et al 2014	2.990	1.410	6.350	5.02
Reeves et al 2015	2.300	1.500	3.550	6.59
Singhal et al 2015	1.010	1.000	1.030	7.78
Aoun et al 2016	1.290	0.870	1.900	6.78
Kang et al 2016	2.920	2.160	3.940	7.15
Shen et al 2017	3.870	1.660	9.010	4.59
D+L pooled ES	1.935	1.458	2.568	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 214.08 (d.f. = 15) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 93.0%
Estimate of between-study variance Tau-squared = 0.2678

Test of ES=1 : z= 4.57 p = 0.000

Figure 5. Forest plot showing the univariate HR (excluding Chernyaev et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Table 5. Univariate HR (excluding Chernyaev et al.)

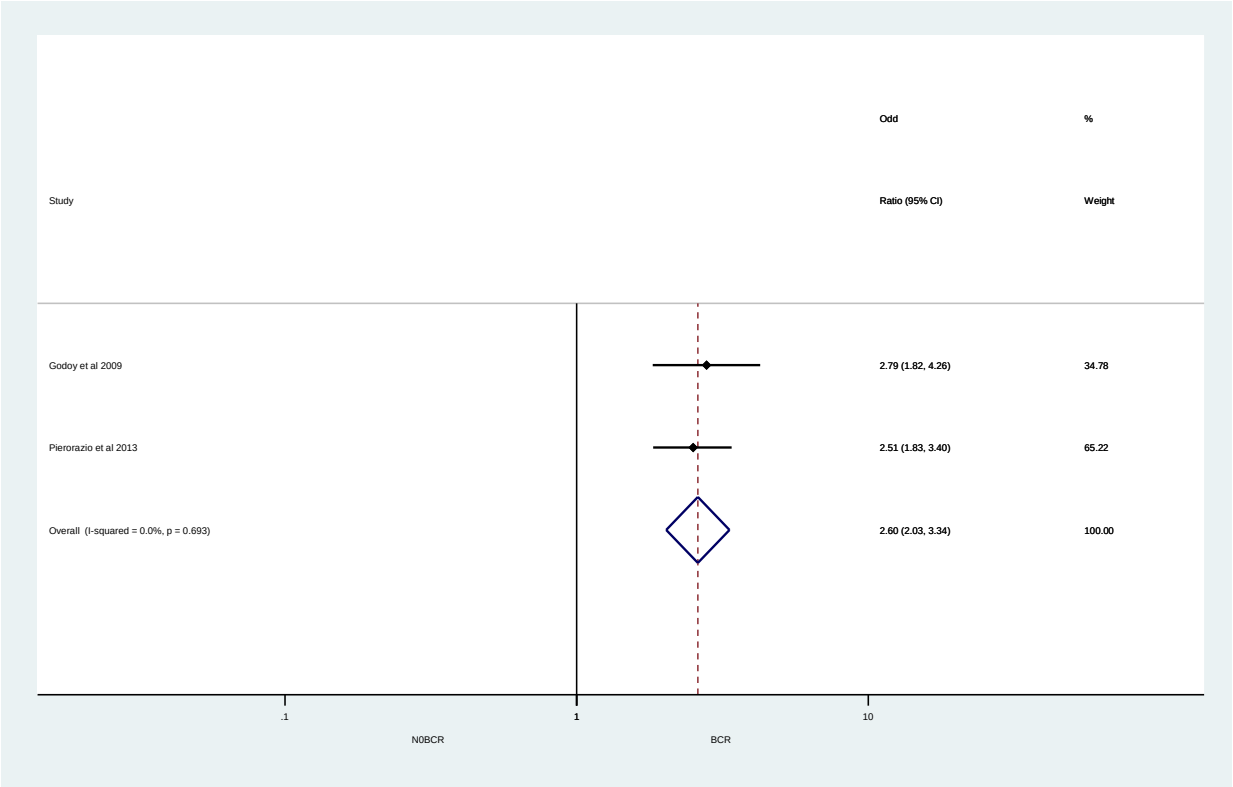
Study	ES	[95% Conf.	Interval]	% Weight
Yu et al 2007	1.710	1.190	2.460	7.23
Jeon et al 2009	2.680	1.640	4.380	6.61
Kumano et al 2009	2.450	1.459	4.115	6.47
Kruser et al 2010	1.970	0.960	4.060	5.42
Jung et al 2011	2.949	1.597	5.445	5.97
Somford et al 2012	2.200	1.400	3.440	6.82
Katz et al 2013	1.940	1.106	3.403	6.24
Miyake et al 2013	1.970	1.638	2.369	7.90
Bittner et al 2013	1.782	1.346	2.360	7.58
Schreiber et al 2014	2.990	1.410	6.350	5.26
Reeves et al 2015	2.300	1.500	3.550	6.91
Singhal et al 2015	1.010	1.000	1.030	8.16
Aoun et al 2016	1.290	0.870	1.900	7.11
Kang et al 2016	2.920	2.160	3.940	7.50
Shen et al 2017	3.870	1.660	9.010	4.81
D+L pooled ES	2.086	1.562	2.786	100.00

```
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared = 209.54 (d.f. = 14) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  93.3%
  Estimate of between-study variance Tau-squared =  0.2670

  Test of ES=1 : z=   4.98 p = 0.000
```

Figure 6. Forest plot showing the univariate OR (excluding Rishtau et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Table 6. Univariate OR (excluding Rishtau et al.)

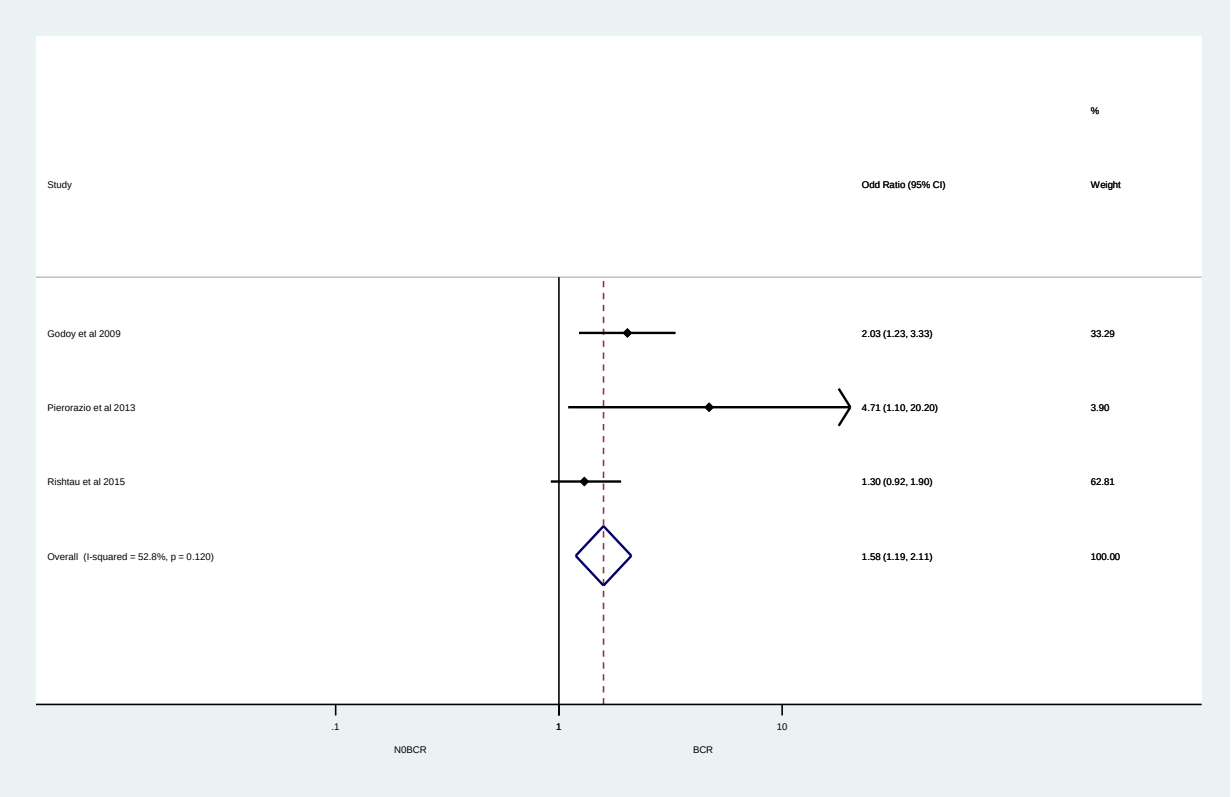
Study	ES	[95% Conf.	Interval]	% Weight
Godoy et al 2009	2.790	1.824	4.260	34.78
Pierorazio et al 201	2.510	1.830	3.400	65.22
I-V pooled ES	2.604	2.028	3.344	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 0.16 (d.f. = 1) p = 0.693
I-squared (variation in ES attributable to heterogeneity) = 0.0%

Test of ES=1 : z= 7.50 p = 0.000

Figure 7. Forest plot showing the univariate OR (including Rishtau et al.)



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Table 7. Univariate OR (including Rishtau et al.)

Study	ES	[95% Conf.	Interval]	% Weight
Godoy et al 2009	2.027	1.230	3.331	33.29
Pierorazio et al 201	4.710	1.100	20.200	3.90
Rishtau et al 2015	1.300	0.920	1.900	62.81
I-V pooled ES	1.585	1.189	2.112	100.00

Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 4.24 (d.f. = 2) p = 0.120
I-squared (variation in ES attributable to heterogeneity) = 52.8%

Test of ES=1 : z= 3.14 p = 0.002

Appendix B: Supplementary Materials

A. Search strategy

Medline/PubMed, National Library of Medicine (1940 – 2018)

Search conducted: 2/13/18

Search:

(((((("Prostatic Neoplasms"[Mesh] OR "Neurotropic cancer"[ALL] OR "Prostate carcinoma"[ALL] OR "Prostatic carcinoma"[ALL] OR "Carcinoma of the prostate"[ALL] OR "Prostatic neoplasms"[ALL] OR "Radical prostatectomy"[ALL] OR "Localized prostate cancer"[ALL])))) AND ("Perineural invasion"[ALL] OR "Perineural invasion density"[ALL] OR "Peripheral zone resection margin"[ALL] OR "Pathological feature on prostate biopsy margin"[ALL]))) AND ((("Biochemical recurrence"[ALL] OR "Biochemical progression"[ALL] OR "Biochemical outcome"[ALL] OR "Biochemical abnormalities"[ALL] OR "biochemical failure"[ALL] OR "Prostate specific Antigen recurrence"[ALL] OR "PSA recurrence"[ALL] OR "Biochemical relapse"[ALL] OR "Prostate specific Antigen failure"[ALL] OR "PSA failure"[ALL] OR "Prostate specific Antigen Progression"[ALL] OR "PSA Progression"[ALL] OR "Tumor recurrence"[ALL] OR "Clinical recurrence"[ALL] OR "Disease free survival"[ALL] OR "Recurrent detectable Prostate specific Antigen"[ALL] OR "Recurrent detectable PSA"[ALL])) OR (("Bone metastasis"[ALL] OR "Spinal metastases"[ALL] OR "Bone metastases"[ALL] OR "Metastatic bone disease"[ALL] OR "Bone marrow metastasis"[ALL])))

#1 AND #2 AND (#3 OR #4)

Final Results: 14

Embase, Elseiver (1948 – 2018)

Search Conducted: 2/13/18

Search:

'prostate cancer'/exp OR 'neurotropic cancer' OR 'prostate carcinoma'/exp OR 'prostatic carcinoma' OR 'prostatic neoplasms' OR 'prostatectomy'/exp OR 'radical prostatectomy' OR 'localized prostate cancer' AND 'perineural invasion'/exp OR 'pni' OR 'perineural invasion density' OR 'peripheral zone resection margin' OR 'pathological feature on prostate biopsy margin' AND ('bone metastasis'/exp OR 'bone metastases' OR 'metastatic bone disease' OR 'spinal metastases' OR 'biochemical recurrence'/exp OR 'biochemical progression' OR 'biochemical outcome' OR 'biochemical abnormalities' OR 'prostate specific antigen recurrence' OR 'psa recurrence' OR 'biochemical relapse' OR 'prostate specific antigen failure' OR 'psa failure' OR 'prostate specific antigen

progression' OR 'psa progression' OR 'tumor recurrence' OR 'clinical recurrence' OR 'disease free survival'/exp OR 'biochemical recurrence free survival'/exp)

#1 AND #2 AND (#3 OR #4)

Final Results: 146

Web of Science, Clarivate Analytics (1900 – 2018)

Search Conducted: 2/13/18

Concept: Prostate Cancer

#1**)** TS=("Prostate cancer" OR "Neurotropic cancer" OR "Prostate carcinoma" OR "Prostatic carcinoma" OR "Carcinoma of the prostate" OR "Prostatic neoplasm*" OR "Radical prostatectomy" OR "Localized prostate cancer")

AND

Concept: PNI

#2) TS=("Perineural Invasion" OR "Perineural invasion density" OR "Peripheral zone resection margin" OR "Pathological feature on prostate biopsy margin")

AND

Concept: Bone Metastasis

#3) TS=("Bone metastasis" OR "Spinal metastases" OR "Bone metastases" OR "Metastatic bone disease" OR "Bone marrow metastasis")

OR

#4) Biochemical recurrence

TS=("Biochemical recurrence" OR "Biochemical progression" OR "Biochemical outcome" OR Biochemical abnormalities" OR biochemical failure" OR "Prostate specific Antigen recurrence" OR "PSA recurrence" OR "Biochemical relapse" OR "Prostate specific Antigen failure" OR "PSA failure " OR "Prostate specific Antigen Progression" OR "PSA Progression" OR "Tumor recurrence" OR "Clinical recurrence" OR "Disease free survival" OR "Recurrent detectable Prostate specific Antigen" OR "Recurrent detectable PSA")

#5) #3 OR #4

Overall Search: #5 AND #2 AND #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=2016-2018

Final Results: 28

Scopus, Elsevier (1970 – 2018)

Search Conducted: 2/13/18

Document search tab: Using article title, abstract, keywords

1. Cifti et al study: **Results 8**

Reference: Ciftci S, Yilmaz H, Ciftci E, Simsek E, Ustuner M, Yavuz U, Muezzinoglu B, Dillioglugil O. Perineural invasion in prostate biopsy specimens is associated with increased bone metastasis in prostate cancer. Prostate [Internet]. 2015;75(15):1783-9.

2. Meng et al meta-analysis: **Results 3**

Meng Y, Liao Y-, Xu P, Wei W-, Wang J. Perineural invasion is an independent predictor of biochemical recurrence of prostate cancer after local treatment: A meta-analysis. Int J Clin Exp Med [Internet]. 2015;8(8):13267-74.

Google Scholar, Google (1791 – 2018)

Search Conducted: February 13, 2018

prostate cancer neutropic carcinoma "perineural invasion" "bone metastasis" "biochemical recurrence "

Results: 3

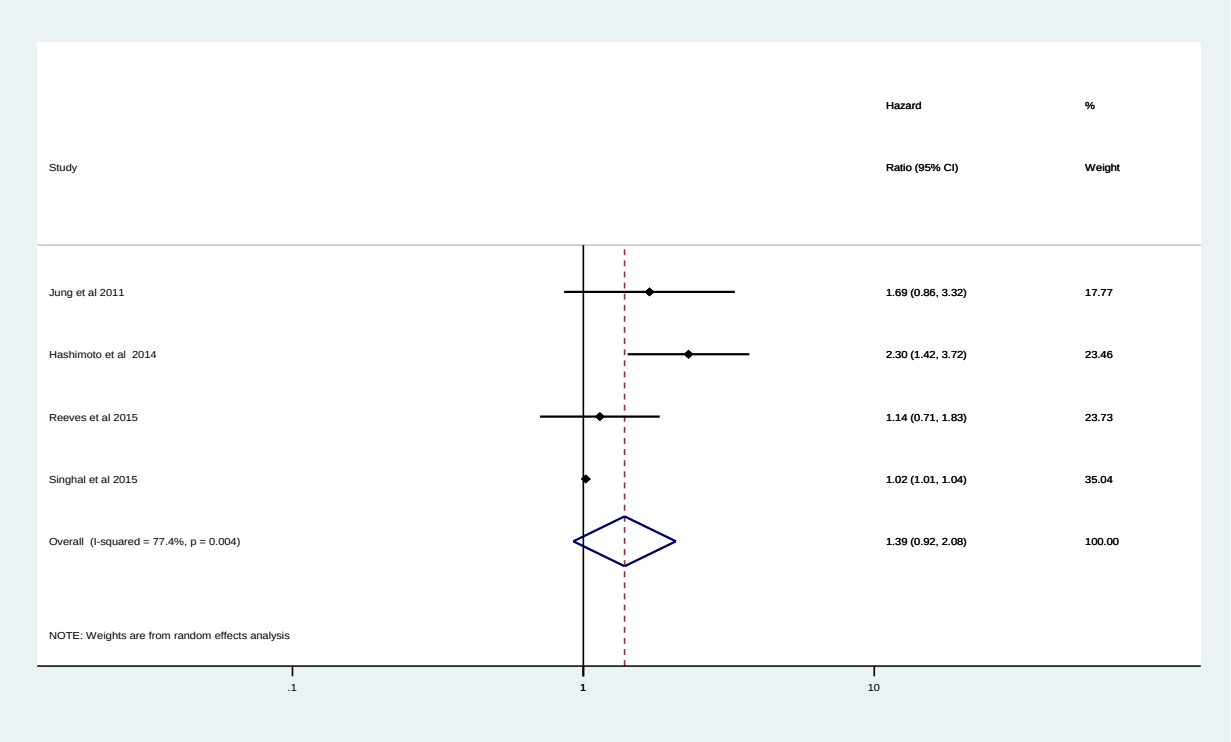
Combined all Results in Endnote Libraries

Removed all the duplicates: 32

Final Total: 170

B. Supplementary Figure 1. Sub-analyses- Forest plots for multivariate HR for 22 studies

Supplementary Figure 1a: Multivariate HR for studies that have a mean follow-up time of less than 2 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Study	ES	[95% Conf.	Interval]	% Weight
Jung et al 2011	1.688	0.859	3.317	17.77
Hashimoto et al 2014	2.300	1.420	3.720	23.46
Reeves et al 2015	1.140	0.710	1.830	23.73
Singhal et al 2015	1.020	1.010	1.040	35.04
D+L pooled ES	1.386	0.924	2.080	100.00

Heterogeneity calculated by formula

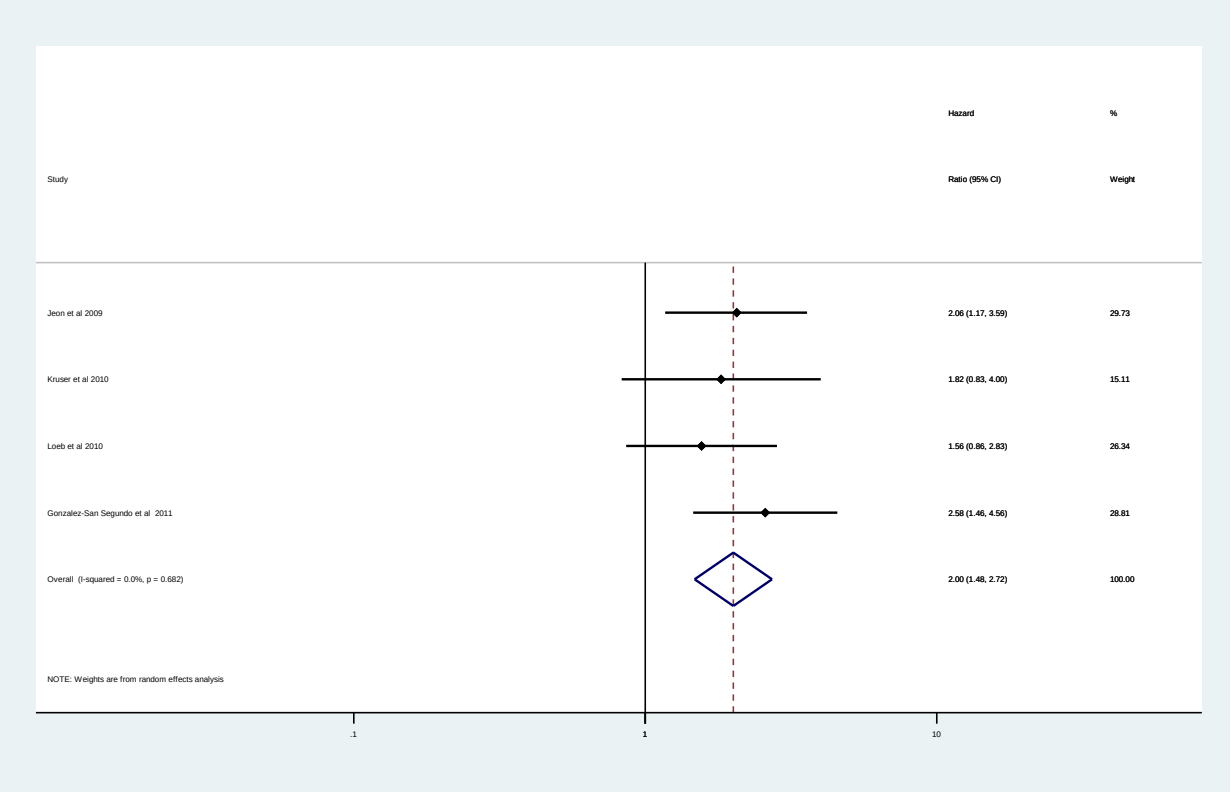
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 13.28 (d.f. = 3) p = 0.004
I-squared (variation in ES attributable to heterogeneity) = 77.4%

```
Estimate of between-study variance Tau-squared =  0.1222

Test of ES=1 : z=   1.58 p = 0.115
```

Supplementary Figure 1b: Multivariate HR for studies that have a mean follow-up time of 2-3 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

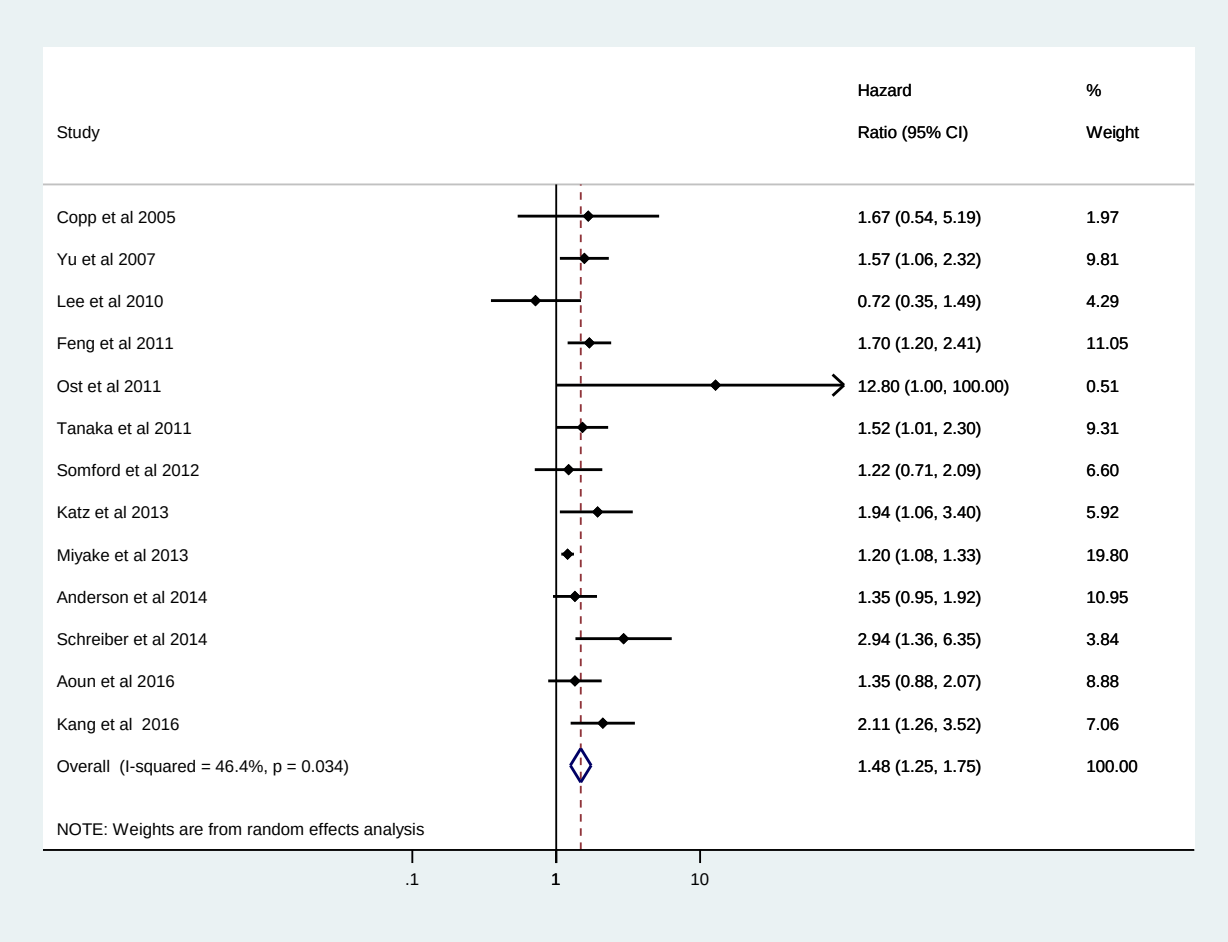
Study	ES	[95% Conf.	Interval]	% Weight
Jeon et al 2009	2.060	1.170	3.590	29.73
Kruser et al 2010	1.820	0.830	4.000	15.11
Loeb et al 2010	1.560	0.860	2.830	26.34
Gonzalez-San Segundo	2.580	1.460	4.560	28.81
D+L pooled ES	2.005	1.477	2.722	100.00

```
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2
```

```
Heterogeneity chi-squared =   1.50 (d.f. = 3) p = 0.682
I-squared (variation in ES attributable to heterogeneity) =0.0%
Estimate of between-study variance Tau-squared =  0.0000

Test of ES=1 : z=   4.46 p = 0.000
```

Supplementary Figure 1c: Multivariate HR for studies that have a mean follow-up time of more than 3 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Study	ES	[95% Conf.	Interval]	% Weight
Copp et al 2005	1.670	0.540	5.190	1.97
Yu et al 2007	1.570	1.060	2.320	9.81
Lee et al 2010	0.718	0.352	1.486	4.29
Feng et al 2011	1.700	1.200	2.410	11.05
Ost et al 2011	12.800	1.000	100.000	0.51
Tanaka et al 2011	1.523	1.010	2.296	9.31
Somford et al 2012	1.220	0.710	2.090	6.60
Katz et al 2013	1.940	1.060	3.403	5.92
Miyake et al 2013	1.200	1.084	1.328	19.80
Anderson et al 2014	1.350	0.950	1.920	10.95
Schreiber et al 2014	2.940	1.360	6.350	3.84
Aoun et al 2016	1.350	0.880	2.070	8.88
Kang et al 2016	2.110	1.260	3.520	7.06
D+L pooled ES	1.482	1.254	1.751	100.00

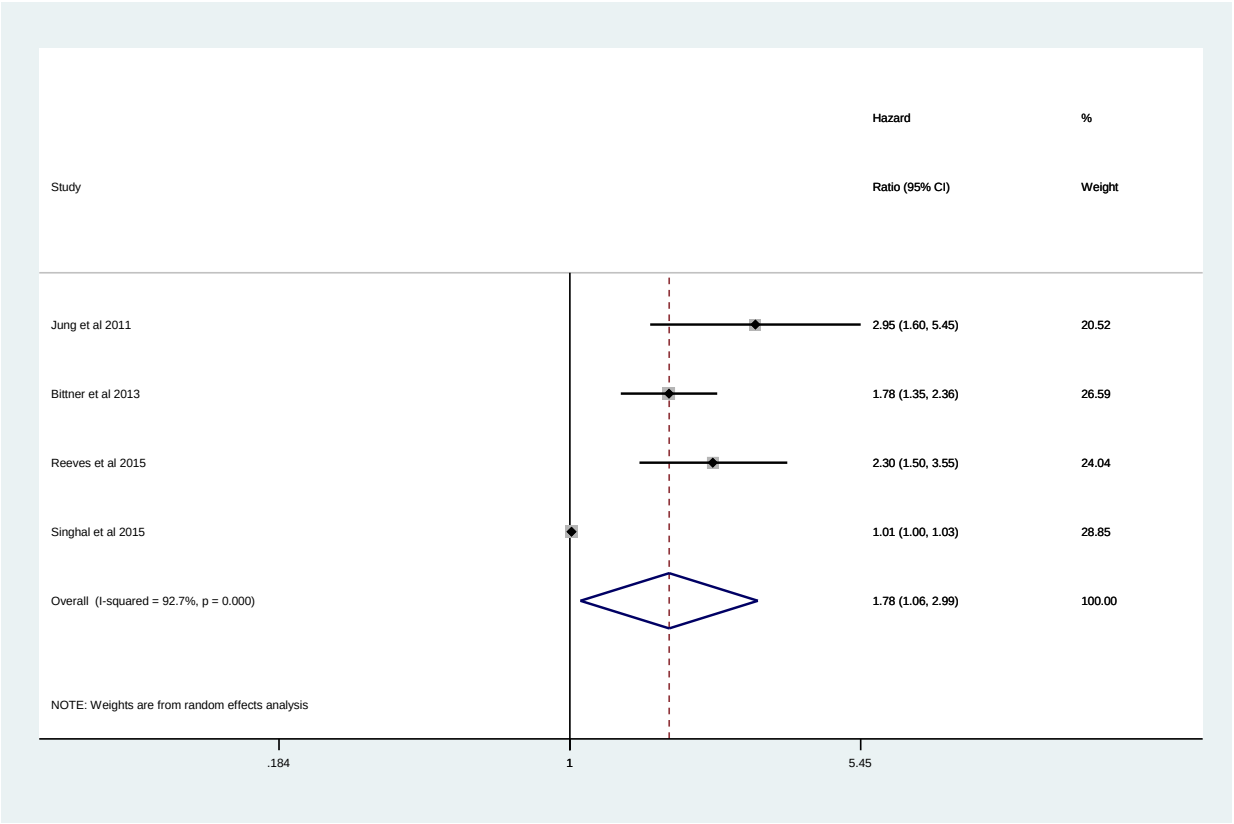
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

Heterogeneity chi-squared = 22.38 (d.f. = 12) p = 0.034
I-squared (variation in ES attributable to heterogeneity)=46.4%
Estimate of between-study variance Tau-squared = 0.0339

Test of ES=1 : z= 4.62 p = 0.000

C. Supplementary Figure 2. Sub-analyses - Forest plots for univariate HR for 16 studies

Supplementary Figure 2a: Univariate HR for studies that have a mean follow-up time of less than 2 years

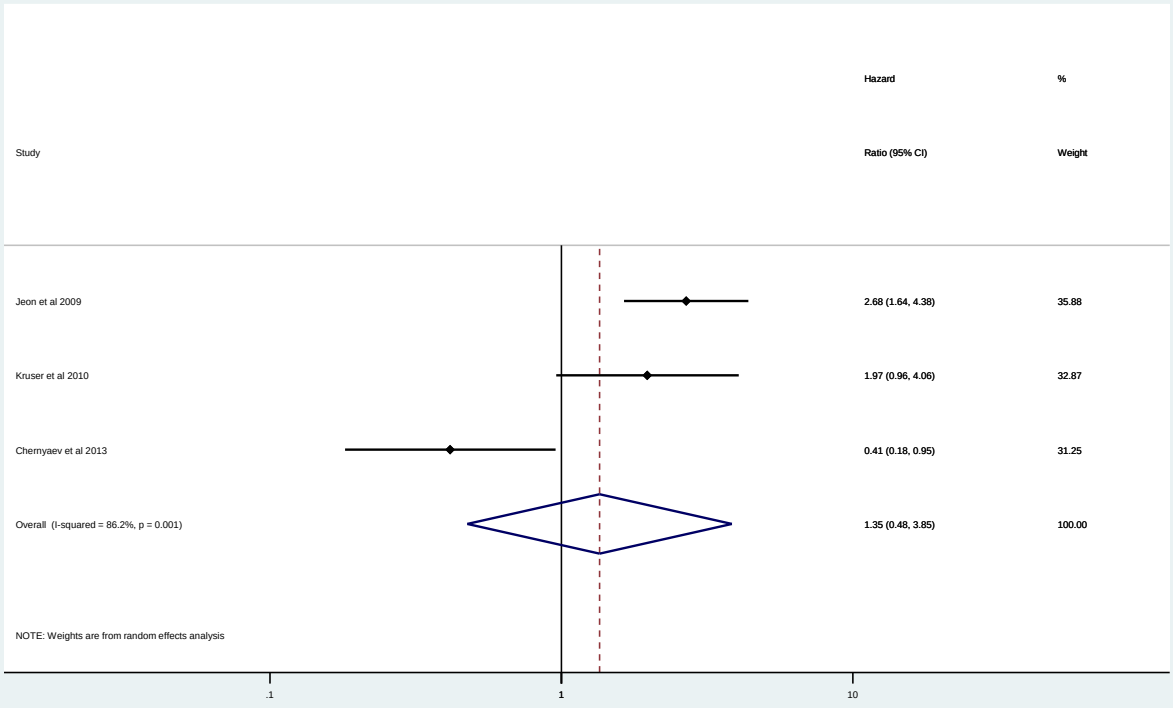


Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

```
           Study     |     ES    [95% Conf. Interval]     %
Weight
---------------------+-------------------------------------------
Jung et al 2011      |  2.949       1.597     5.445         20.52
Bittner et al 2013   |  1.782       1.346     2.360         26.59
Reeves et al 2015    |  2.300       1.500     3.550         24.04
Singhal et al 2015   |  1.010       1.000     1.030         28.85
---------------------+-------------------------------------------
D+L pooled ES        |  1.784       1.064     2.991        100.00
---------------------+-------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  41.29 (d.f. = 3) p = 0.000
  I-squared (variation in ES attributable to heterogeneity)=92.7%
  Estimate of between-study variance Tau-squared =  0.2411
  Test of ES=1 : z=   2.19 p = 0.028
```

Supplementary Figure 2b: Univariate HR for studies that have a mean follow-up time of 2-3 years



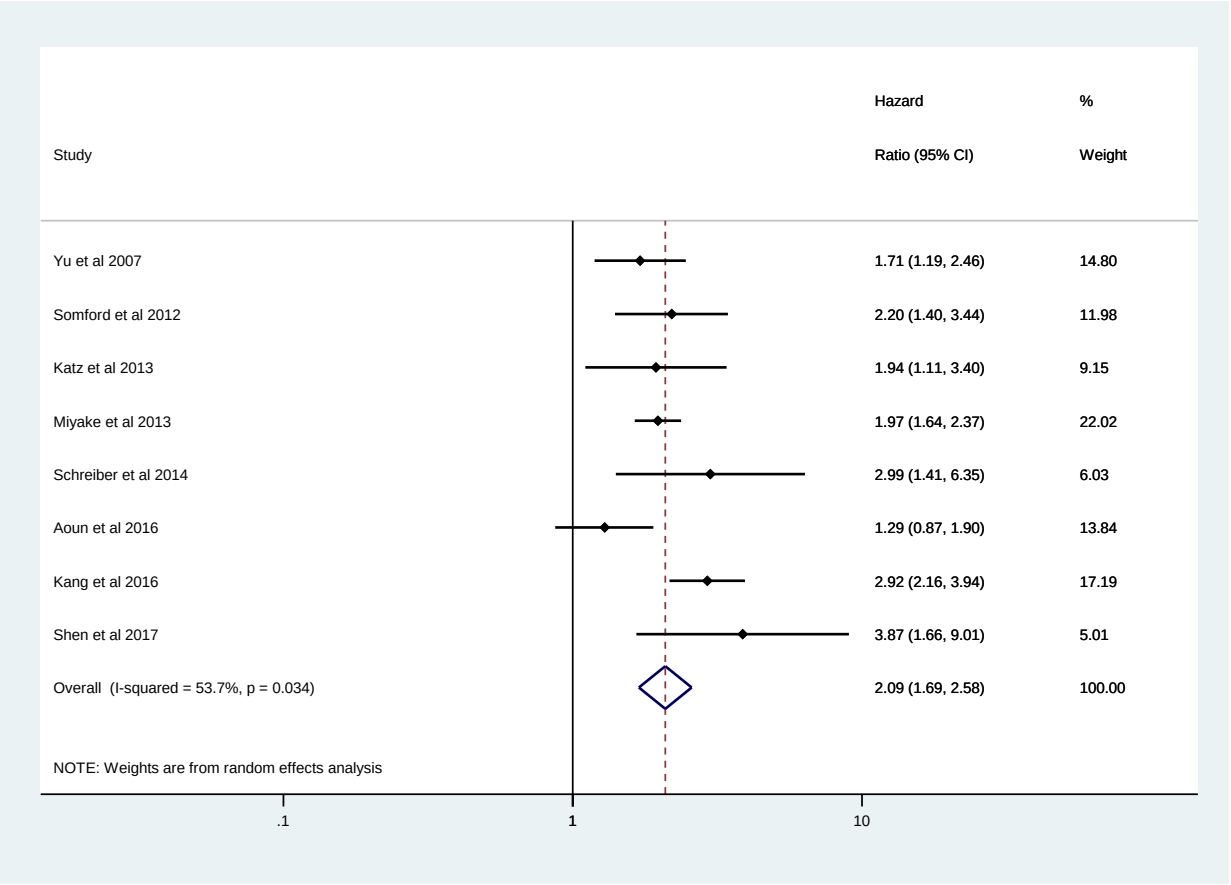
Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

```
          Study     |     ES    [95% Conf. Interval]     %
Weight
----------------------+-----------------------------------------
Jeon et al 2009       |  2.680       1.640     4.380         35.88
Kruser et al 2010     |  1.970       0.960     4.060         32.87
Chernyaev et al 2013  |  0.415       0.181     0.955         31.25
----------------------+-----------------------------------------
D+L pooled ES         |  1.352       0.475     3.845        100.00
----------------------+-----------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  14.50 (d.f. = 2) p = 0.001
  I-squared (variation in ES attributable to heterogeneity)=86.2%
  Estimate of between-study variance Tau-squared =  0.7297

  Test of ES=1 : z=   0.57 p = 0.572
```

Supplementary Figure 2c: Univariate HR for studies that have a mean follow-up time of more than 3 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

Study	ES	[95% Conf.	Interval]	% Weight
Yu et al 2007	1.710	1.190	2.460	14.80
Somford et al 2012	2.200	1.400	3.440	11.98
Katz et al 2013	1.940	1.106	3.403	9.15
Miyake et al 2013	1.970	1.638	2.369	22.02
Schreiber et al 2014	2.990	1.410	6.350	6.03
Aoun et al 2016	1.290	0.870	1.900	13.84
Kang et al 2016	2.920	2.160	3.940	17.19
Shen et al 2017	3.870	1.660	9.010	5.01
D+L pooled ES	2.089	1.694	2.578	100.00

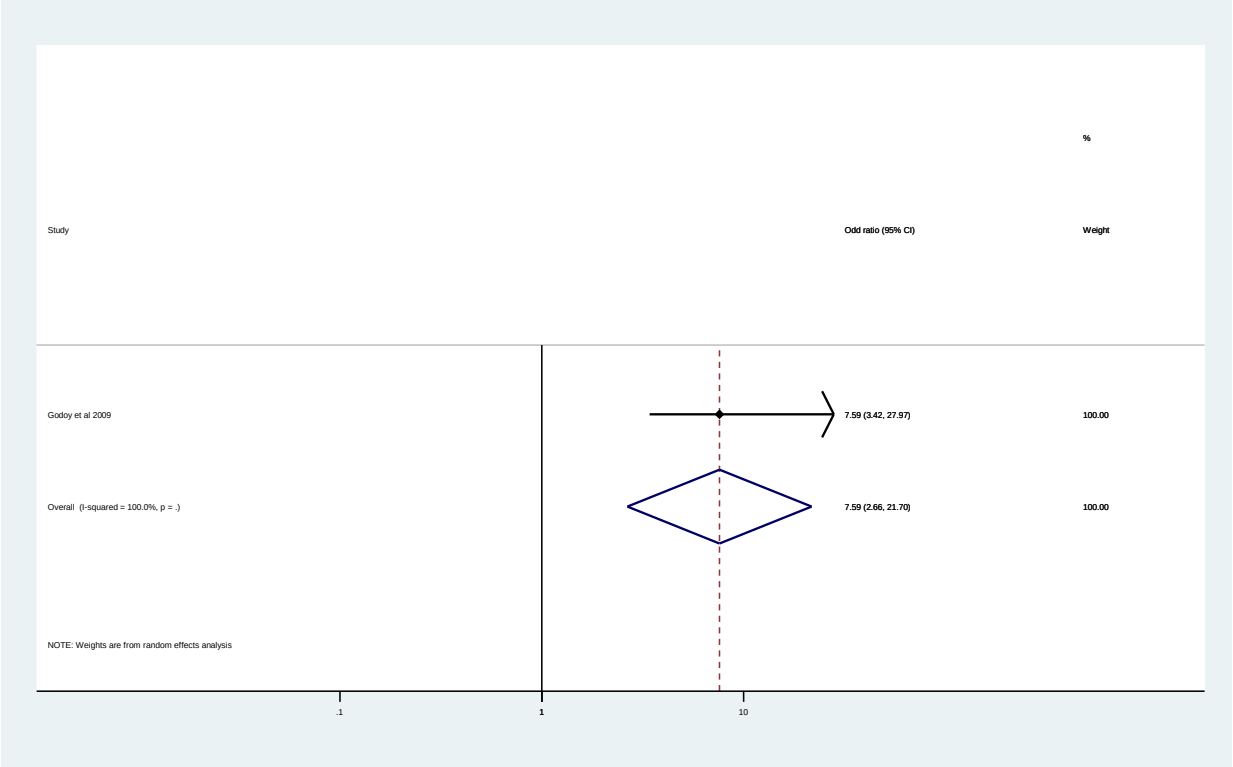
Heterogeneity calculated by formula
Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

```
Heterogeneity chi-squared =  15.13 (d.f. = 7) p = 0.034
I-squared (variation in ES attributable to heterogeneity)=53.7%
Estimate of between-study variance Tau-squared =  0.0434

Test of ES=1 : z=   6.87 p = 0.000
```

D. **Supplementary Figure 3.** Sub-analyses Funnel plot for univariate OR for 3 studies

Supplementary Figure 3a: Univariate OR for studies with a mean follow-up of 2-3 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval;

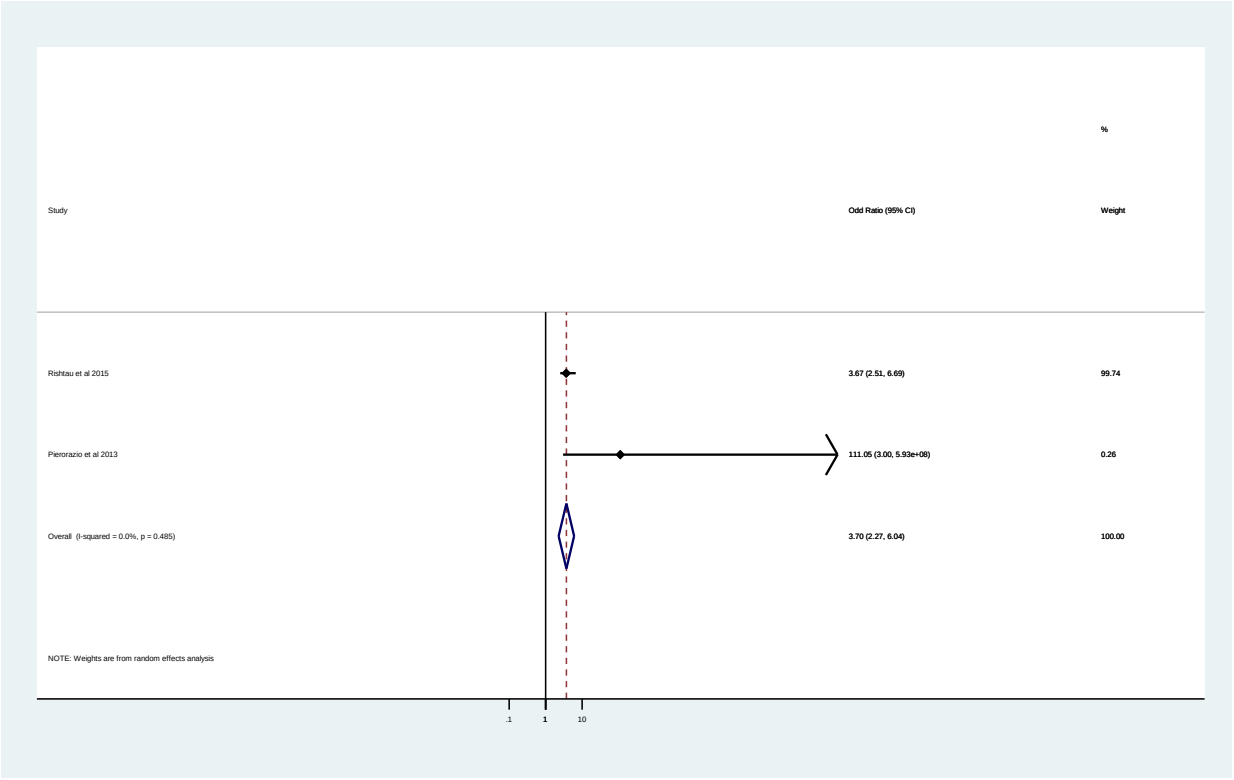
squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

```
          Study     |     ES    [95% Conf. Interval]     %
Weight
----------------------+-------------------------------------------
Godoy et al 2009      |  7.591       3.421    27.966        100.00
----------------------+-------------------------------------------
D+L pooled ES         |  7.591       2.655    21.704        100.00
----------------------+-------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2
```

```
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    0.000
  I-squared (variation in ES attributable to heterogeneity) =0.0

  Test of ES=1 : z=   3.78 p = 0.000
```

Supplementary Figure 3b: Univariate OR for studies with a mean follow-up of more than 3 years



Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval;

squares, risk ratios; diamonds, pooled risk ratios. Abbreviations: CI, Confidence interval.

```
           Study     |     ES    [95% Conf. Interval]     %
Weight
---------------------+-----------------------------------------
Rishtau et al 2015   |  3.669       2.509     6.686         99.74
Pierorazio et al 201 |111.052       3.004    5.9e+08         0.26
---------------------+-----------------------------------------
D+L pooled ES        |  3.702       2.270     6.039        100.00
---------------------+-----------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   0.49 (d.f. = 1) p = 0.485
  I-squared (variation in ES attributable to heterogeneity) =0.0%
  Estimate of between-study variance Tau-squared =  0.0000

  Test of ES=1 : z=   5.24 p = 0.000
```

Supplementary Table 1. PRISMA check list

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p. 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p. 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p. 7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p. 9-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p. 9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary materials (31-33)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p. 9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p. 9-10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 9-10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p. 10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	p. 10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p. 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p. 10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 (p.16)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p. 10, Figures 2-3, Tables 2-3, Figures 4-5, Tables 4-5, Figures 6-7, Tables 6-7 (p. 19-29)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-3, Tables 2-3, Figures 4-5, Tables 4-5, Figures 6-7, Tables 6-7 (p. 19-29)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	p. 12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p. 10, Figures 2-3, Tables 2-3, Figures 4-5, Tables 4-5, Figures 6-7, Tables 6-7 (p. 19-29)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p. 13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	p. 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p. 14-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

Supplementary Table 2. Characteristics of excluded full-text articles

Excluded study	Reason of exclusion
Anderson 2017	No univariate or multivariate analyses performed for PNI
Brimo 2008	No univariate or multivariate analyses performed for PNI
Celik 2018	No univariate or multivariate analyses performed for PNI
Ceylan 2018	No univariate or multivariate analyses performed for PNI
DellAtti 2016	No univariate or multivariate analyses performed for PNI
Desmeules 2015	PNI not recorded for RP
Flood 2016	No univariate or multivariate analyses performed for PNI
Freedland 2002	PNI not recorded for RP
Godoy 2011	Only analyzed positive surgical margin relationship to BCR
Kincius 2011	No univariate or multivariate analyses performed for PNI
Kurahasi 2010	No univariate or multivariate analyses performed for PNI
La Roca 2014	Only analyzed positive surgical margin relationship to BCR
Lee 2014	No univariate or multivariate analyses performed for PNI
Miyake 2006	PNI not recorded for RP
Nelson 2003	No univariate or multivariate analyses performed for PNI
Ng 2012	PNI not recorded for RP
Ngo 2013	PNI not recorded for RP
Ohno 2013	PNI not recorded for RP
Olar 2014	PNI not recorded for RP
Perez-Martinez 2008	No univariate or multivariate analyses performed for PNI
Pina 2010	PNI not recorded for RP
Quintal 2011	PNI not recorded for RP
Ramsden 2004	No univariate or multivariate analyses performed for PNI
Simsir 2011	No univariate or multivariate analyses performed for PNI
Turpin-Wendling 2006	Language of publication (French)
Weight 2006	PNI not recorded for RP

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4. Paller *et al*: Management of Biochemically Recurrent Prostate Cancer After Local Therapy: Evolving Standards of Care and New Directions. *Clin Adv Hematol Oncol*. 2013; 11(1): 14-23. Print.
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13. Feng *et al*: Perineural invasion predicts increased recurrence, metastasis and death from prostate cancer following treatment with dose-escalated radiation therapy. *Int J. Radiation Oncology Biol Phys*. 2011; 81(4): e361-e367. Print.
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