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Original Article

Do tumor volume, percent tumor volume predict biochemical recurrence after radical prostatectomy? A meta-analysis

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Abstract: The aim of this meta-analysis was to explore the effects of tumor volume (TV) and percent tumor volume (PTV) on biochemical recurrence (BCR) after radical prostatectomy (RP). An electronic search of Medline, Embase and CENTRAL was performed for relevant studies. Studies evaluated the effects of TV and/or PTV on BCR after RP and provided detailed results of multivariate analyses were included. Combined hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models. A total of 15 studies with 16 datasets were included in the meta-analysis. Our study showed that both TV (HR 1.04, 95% CI: 1.00-1.07; P=0.03) and PTV (HR 1.01, 95% CI: 1.00-1.02; P=0.02) were predictors of BCR after RP. The subgroup analyses revealed that TV predicted BCR in studies from Asia, PTV was significantly correlative with BCR in studies in which PTV was measured by computer planimetry, and both TV and PTV predicted BCR in studies with small sample sizes (<1000). In conclusion, our meta-analysis demonstrated that both TV and PTV were significantly associated with BCR after RP. Therefore, TV and PTV should be considered when assessing the risk of BCR in RP specimens.

Keywords: Tumor volume, percent tumor volume, prostate cancer, biochemical recurrence

Introduction

Prostate cancer is the most commonly diagnosed tumor in American men, nearly 233000 men were newly diagnosed with prostate cancer, and the number of cancer-specific deaths were estimated to be 29480 in America in 2014 [1]. Radical prostatectomy (RP) has shown a cancer-specific survival benefit for men with early stage prostate cancer [2]. However, the risk of biochemical recurrence (BCR) after RP is nearly 30%, and the patients with BCR had poorer long-term survivals [3]. Several studies reported that preoperative prostate-specific antigen (PSA) level, pathological tumor stage (pT stage), positive surgical margin, Gleason's score, seminal vesicle invasion, lymph node invasion, extracapsular extension were independent predictors of BCR after RP [3-7]. And as tumor volume (TV) was significantly correlative with these pathologic parameters, including pT stage, Gleason score and positive surgical margin [4, 8-10], TV and percent tumor volume (PTV, the percentage of prostate volume involved with tumor) might be predictors of BCR [6, 11, 12]. While in some other studies, opposite results were reported [13-15]. The aim of this meta-analysis was to evaluate the effects of TV and PTV on BCR after RP, which could help in assessing the risk of BCR after RP and directing further treatment.

Materials and methods

Search strategy

We conducted an electronic search of Medline, Embase and CENTRAL for all relevant studies (the last search update was January 16, 2015), using the following search terms: (tumor volume OR cancer volume OR tumor percent involvement OR tumor percentage involvement OR percent cancer OR tumor percentage) and (recurrence OR relapse OR PSA failure OR biochemical failure OR PSA progression OR biochemical progression) and prostatectomy. The search was limited to English language.

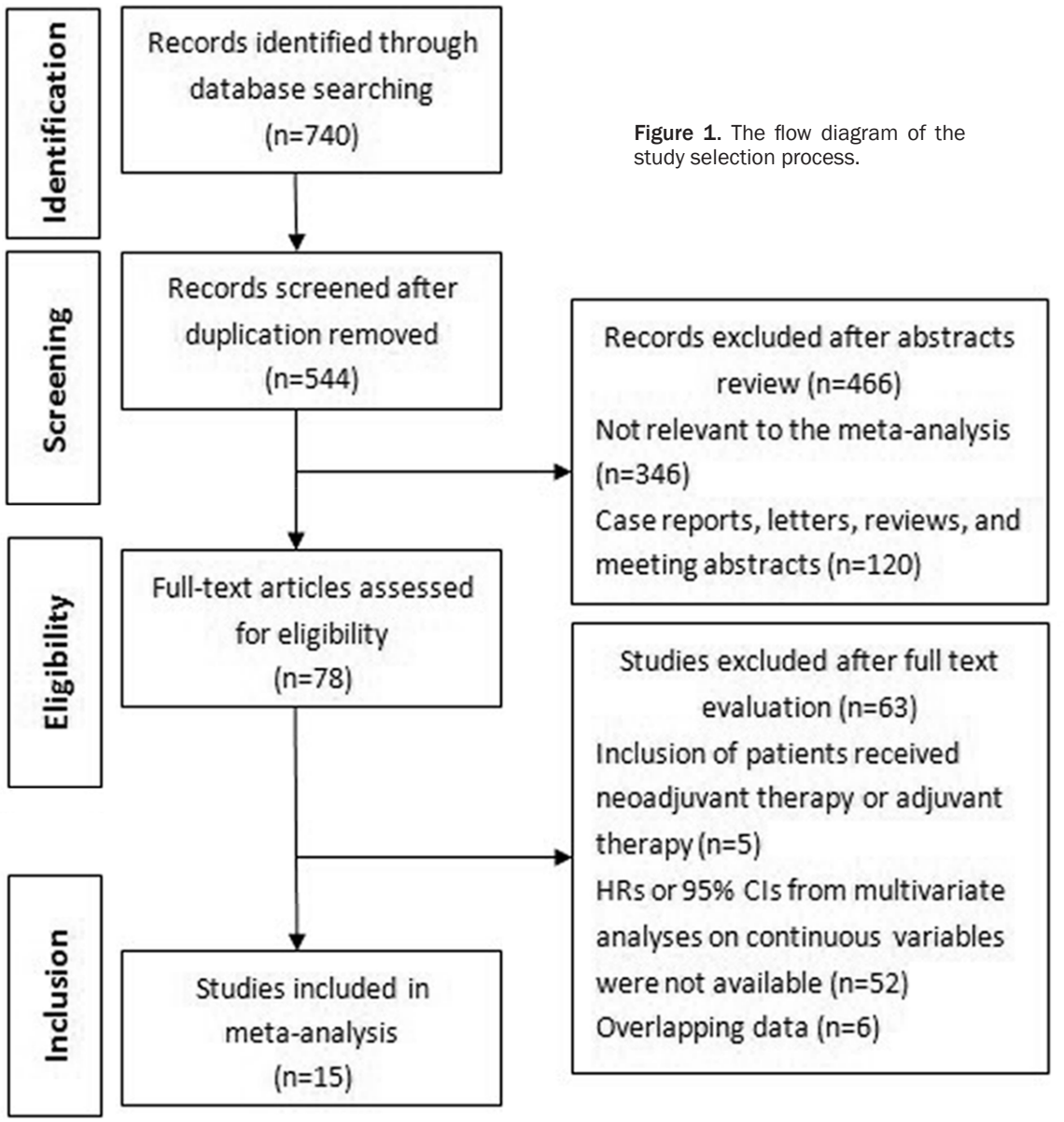

Figure 1. The flow diagram of the study selection process.

Selection criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, the Population, Intervention, Comparison, Outcome, and Study design (PICOS) eligibility criteria were applied to define study eligibility [16]. The studies reported the effects of TV and/or PTV on BCR after RP were considered relevant to this meta-analysis. And these included studies must meet the following criteria: (a) Studies that excluded patients received neoadjuvant therapy or adjuvant therapy; (b) Studies that regarded TV and/or PTV as a continuous variable (ml, %) and provided hazard ratios (HRs) from multivariate Cox proportional hazards regression model analyses with their corresponding 95% confidence intervals (CIs). Case reports, letters, review articles, meeting abstracts, comments were excluded during the process of study selection. For studies that reported results of the same or overlapping data, only the study with the largest number of patients was included.

Study selection process

Relevant abstracts through databases search were screened after removing duplicates; case reports, letters, review articles, meeting

Table 1. The characteristics and quality assessments of included studies

Studies	Study location	Study design	Mean/ median age	No. of patients	No. of BCR (%)	Median/ mean follow-up, mo	Recruit-ment period	Definition of BCR	Mean/median TV or PTV, ml or %	Evaluation methods	Adjusted for	Risk factors	Quality assessment
Wolters et al (2010) [20]	The Nether-lands	P	63.6/64	344	57 (16.6%)	98/-	1993-2000	PSA >0.2 ng/ml	1.05/0.66, -	Computer planimetry	1, 3, 4, 5, 7	TV, PTV	********
Uhlman et al (2010) [21]	USA	P	62.3/-	3528	988 (28.1%)	-	1988-2008	PSA >0.2 ng/ml	-	Visual estimation	2, 3, 4, 5, 7	TV, PTV	*******
Cho et al (2011) [22]	Korea	R	64.5/-	259	59 (22.8%)	40.0/-	2005-2010	PSA ≥0.2 ng/ml and rising	5.94/-, 18.27/-	Visual estimation	2, 3, 5, 6, 7,	TV, PTV	*******
Thompson (w)* et al (2011) [23]	USA	R	59.7/-	478	-	44.8/-	2000-2003	PSA ≥0.2 ng/ml and confirming	-/1.67, -	Computer planimetry	3, 4, 5, 6, 8	TV, PTV	*******
Thompson (s)* et al (2011) [23]	USA	R	60.9/-	1269	-	17.3/-	2003-2008	PSA ≥0.2 ng/ml and confirming	-/4.2, -	Visual estimation	3, 4, 5, 6, 8	TV, PTV	*******
Hong et al (2010) [24]	Australia	R	61.9/-	269	64 (24%)	12/-	2005-2009	PSA ≥0.4 ng/ml	/3.7, -	Computer planimetry	2, 3, 4, 5, 6, 7	TV, PTV	*******
Hinkelammert et al (2014) [25]	Germany	R	-/64	758	152 (20.1%)	63/-	2000-2005	PSA >0.1 ng/ml and rising	7.5/5.28, 15.3/11.5	Computer planimetry	1, 2, 3, 4, 7, 12	TV, PTV	*******
Park et al (2011) [26]	Korea	R	-/67	158	30 (19.0%)	24.0/-	2005-2007	PSA ≥ 0.2 ng/ml	2.07/-	Visual estimation	2, 3, 6, 9, 10, 16, 18	TV	*******
Loeb et al (2012) [27]	The Nether-lands	P	63.6/-	474	69 (14.6%)	119.0/-	1993-1999	PSA >0.2 ng/ml	1.3/-	Visual estimation	3, 4, 19	TV	********
Kim et al (2013) [28]	Korea	R	64.3/-	1129	186 (16.5%)	37.0/-	2005-2011	PSA >0.2 ng/ml and rising	1.5/-	Visual estimation	1, 2, 3, 5, 6, 7, 11	TV	*******
Huang et al (2013) [29]	Austria	P	-	1048	146 (13.9%)	18/-	2003-2011	PSA ≥0.2 ng/ml and rising	/2.1	computer planimetry	2, 3, 4, 5, 6, 7	TV	******
Marks et al (2007) [30]	USA	R	-/64	174	87 (50.0%)	-/37	1990-1998	PSA ≥0.1 ng/ml	/30	Visual estimation	2, 3, 4, 17	PTV	*******
Song et al (2013) [31]	Korea	R	64.7/-	404	39 (9.7%)	-/52.5	2000-2007	PSA >0.2 ng/ml and rising	12.1/-	Computer planimetry	2, 3, 7	PTV	*******
Leng et al (2013) [32]	Korea	R	-/67	167	44 (26.3%)	-/33.7	2005-2010	PSA >0.2 ng/ml	-	Visual estimation	2, 3, 7, 8, 9, 14	PTV	*******
Hansen et al (2014) [33]	Germany	R	65/66	595	99 (16.6%)	12/34	1992-2011	PSA ≥0.2 ng/ml and rising	-	Visual estimation	2, 3, 4, 7, 8, 13	PTV	*******
You et al (2014) [34]	Korea	R	64.7/-	397	199 (50.1%)	76/-	2000-2009	PSA ≥0.2 ng/ml and confirming	19.9/-	Computer planimetry	2, 3, 4, 7, 8	PTV	*******

P: prospective cohort study. R: retrospective study. PSA: prostate-specific antigen. Adjusted for: 1, age; 2, preoperative PSA level; 3, Gleason score; 4, pathological stage; 5, seminal vesicle invasion; 6, extracapsular extension; 7, surgical margin status; 8, lymphovascular invasion; 9, perineural invasion; 10, clinical stage; 11, body-mass index; 12, tumor foci; 13, percent high-grade tumor volume; 14, PSA density; 15, prostate volume; 16, percent of positive biopsy cores; 17, extent of margin positivity; 18, tumor size; 19, screening group. *Thompson (w) and Thompson (s) means two datasets from the two groups: Whole-mount group and Systematic sampling group in the study by Thompson et al [23].

Table 2. Main results of meta-analysis for the effect of TV on BCR after RP

Groups/subgroups	Stuies, n	Heterogeneity test		Test for overall effect		
		I^2, %	*P*	HR	95% CI	*P*
Overall	11	69	<0.01	1.04	1.00-1.07	0.03
Study location						
USA	3	55	0.11	1.02	0.98-1.06	0.38
Europe	3	89	<0.01	1.07	0.90-1.27	0.42
Asia	3	0	0.62	1.08	1.00-1.17	0.04
Australia	2	58	0.12	1.03	0.97-1.10	0.28
Evaluation methods						
Computer planimetry	5	62	0.03	1.02	0.99-1.06	0.20
Visual estimation	6	76	<0.01	1.08	1.00-1.17	0.06
Sample size						
≥1000	4	2	0.38	1.00	0.98-1.03	0.82
<1000	7	79	<0.01	1.06	1.01-1.12	0.03

abstracts, comments and other irrelevant records were excluded. The remaining records were assessed for eligibility based on full-text articles evaluation. In addition, the references of included studies were also examined for potential relevant studies. In the end, the studies were selected according to previously mentioned inclusion criteria.

Study quality assessment

As all the finally included studies were nonrandomized studies, the quality of these studies were assessed according to the Newcastle-Ottawa scale [17], which was recommended by the Cochrane Collaboration. Stars were allocated to each study in the range of 0 to 9, and the studies with 6 or more stars were deemed of high quality.

Data extraction

Two authors (Y.M. and H.L.) extracted data from all of the included studies independently. The following information was extracted: year of publication, study location, study design, population characteristics, incidence of BCR, definition of BCR, median follow-up period, data of TV and PTV, HRs of multivariate analyses with their corresponding 95% CIs and covariates in multivariate analyses. Any discrepancy was resolved by discussion.

Statistical analyses

We performed the meta-analysis about the effects of TV and PTV on BCR after RP using HRs and their corresponding 95% CIs as effect measures. Cumulative effects of TV and PTV were assessed by the generic inverse variance method [18]. Pooled HRs and their corresponding 95% CIs were used to evaluate the effect of TV or PTV on BCR after RP, and values of $P<0.05$ were considered statistically significant. Between-study heterogeneity was assessed using both Q test and I^2 statistics. A value of $P<0.10$ for Q test or an I^2 statistics >50% was considered significant. A random-effects model would be used if heterogeneity was significant; otherwise a fixed-effects model would be used [19]. Subgroup analyses were conducted according to study location, estimation method and sample size. Sensitivity analysis was carried out to assess the quality and stability of the results by calculating the pooled HRs when omitting one study each time. The potential publication bias was assessed with funnel plot and Egger's test. All statistical analyses were performed with RevMan 5.3 software and STATA 12 software. *P* values for all analyses were two-sided.

Results

Characteristics of eligible studies

A total of 15 studies [20-34] were included in this meta-analysis. The flow chart of study selection is showed in **Figure 1**. There were 16 eligible studies in the meta-analysis for one study [23] provided data of two groups with different specimens, and we dealt with them independently. Of the 16 studies, 4 were prospective cohort studies, 12 were retrospective studies, and all these included studies were considered of high quality. A total of 11 studies with 9714 patients in regarding to TV and 12 studies with 8642 patients for PTV were respectively included in the meta-analysis. The characteristics and quality assessments of eligible studies were summarized in **Table 1**. The incidence of BCR after RP ranged from 9.7% to 50.1% according to the studies.

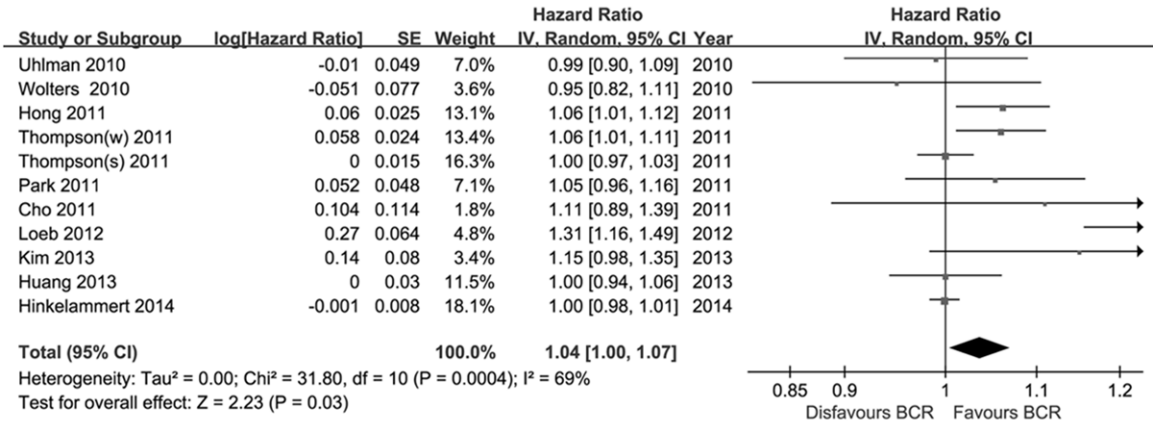

Figure 2. Forest plot of TV and BCR risk after RP.

Table 3. Main results of meta-analysis for the effect of PTV on BCR after RP

Groups/subgroups	Stuies, n	Heterogeneity test		Test for overall effect		
		I^2, %	*P*	HR	95% CI	*P*
Overall	12	68	<0.01	1.01	1.00-1.02	0.02
Study location						
USA	4	78	<0.01	1.01	0.99-1.04	0.38
Europe	3	42	0.18	1.01	1.00-1.02	0.24
Asia	4	71	0.02	1.02	1.00-1.05	0.09
Australia	1	-	-	1.02	1.00-1.03	0.02
Evaluation methods						
Computer planimetry	6	51	0.07	1.02	1.01-1.03	<0.01
Visual estimation	6	59	0.03	1.00	0.99-1.02	0.76
Sample size						
≥1000	2	89	<0.01	1.07	0.93-1.23	0.37
<1000	10	63	<0.01	1.01	1.00-1.02	0.02

TV

In 11 studies, TV was assessed as a potential predictor of BCR. Mean TV ranged from 1.05 ml to 7.5 ml. A meta-analysis demonstrated that TV (HR 1.04, 95% CI: 1.00-1.07; P=0.03, I^2=69%) was a predictor of BCR after RP. The results were showed in **Table 2** and **Figure 2**. Then we performed subgroup analyses according to study location, estimation method and sample size (≥1000, <1000). TV was found significantly correlated with BCR in studies from Asia (HR 1.08, 95% CI: 1.00-1.17; P=0.04, I^2=0%), and studies with small sample sizes (<1000) (HR 1.06, 95% CI: 1.01-1.12; P=0.03, I^2=79%). No significant correlations were found in the remaining subgroup analyses (all P>0.05) (**Table 2**).

PTV

PTV as a potential predictor of BCR was reported in 12 studies. Our study revealed that PTV (HR 1.01, 95% CI: 1.00-1.02; P=0.02, I^2=68%) was a predictor of BCR after RP (**Table 3** and **Figure 3**). Then subgroup analyses were performed by study location, estimation method and sample size (≥1000, <1000). A significant correlation between PTV and BCR was found in studies in which PTVs were measured by computer planimetry (HR 1.02, 95% CI: 1.01-1.03; P<0.01, I^2=51%). Still, significant correlation was found in studies with small sample sizes (<1000) (HR 1.01, 95% CI: 1.00-1.02; P=0.02, I^2=63%). In terms of study location, the only study [24] from Austria showed PTV was significantly related with BCR (HR 1.02, 95% CI: 1.00-1.05; P=0.02). Results of the remaining subgroup analyses showed no relation between PTV and BCR (all *P*>0.05) (**Table 3**).

Sensitivity and publication bias analysis

Sensitivity analysis revealed that our results were statistically stable. The potential publication bias was assessed with funnel plots and Egger's test. Both funnel plots and Egger's test (P=0.054 for TV, P=0.160 for PTV) showed no obvious publication bias in our meta-analysis.

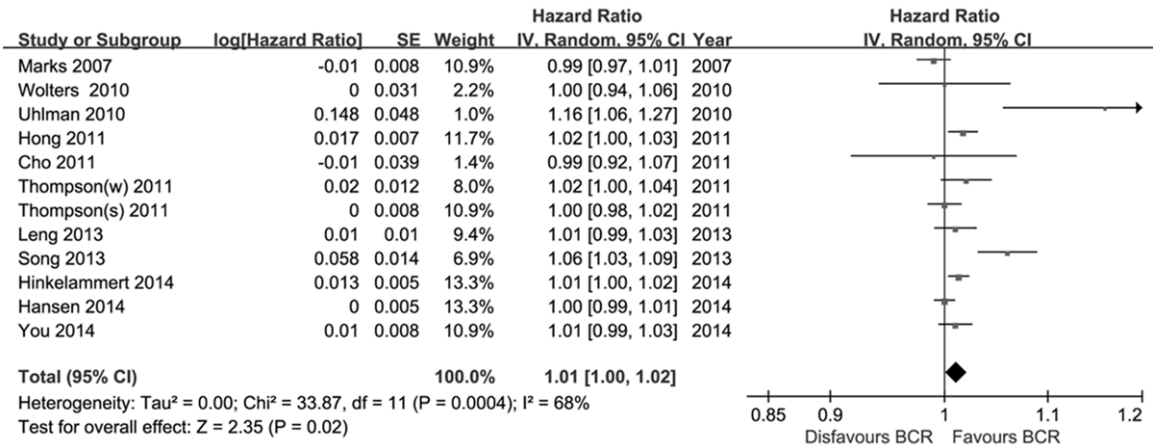

Figure 3. Forest plot of PTV and BCR risk after RP.

Discussion

The incidence of BCR after RP was relatively high, and long-term survivals of the patients with BCR were poor [3]. Whether TV or PTV was a predictor of BCR after RP was still controversial according to the studies. Hence, we conducted this present meta-analysis. Our results showed that both TV and PTV predicted BCR after RP. To our knowledge, this is the first meta-analysis exploring the effects of TV and PTV on BCR after RP.

Fifteen studies were included in our meta-analysis, with one of which [23] providing two datasets, which were dealt with independently. Hence, a total of 16 studies (11 for TV, 12 for PTV) were included at last. Overall, we found that both TV and PTV were significant independent predictors of BCR after RP. The low HRs for TV and PTV might result from the small changes in measured TV (1 ml) and PTV (1%). In the subgroup analyses according to study location, a significant association was found between TV and BCR in studies from Asia, while those subgroup analyses in other areas showed negative results, which means ethnic origin might affect the results. For PTV, the only study from Austria revealed a significant correlation between PTV and BCR; while there were no significant correlations in the remaining subgroups including studies from other areas. In terms of different assessment methods, neither TV measured by computer planimetry nor TV measured by visual estimation predicted BCR after RP. However, PTV evaluated by computer planimetry was a significant predictor of BCR after RP, while PTV evaluated by visual estimation was not. The possible explanation was that computer planimetry could be more accurate than visual estimation, which showed more prognostic values of TV and PTV [23]. Subgroup analyses based on sample size showed that both TV and PTV had significant impacts on BCR in those studies with small sample sizes (<1000), but not in studies with large sample sizes (≥1000). Generally, the studies with large sample sizes would have greater power than those with small sample sizes. It seemed that neither TV nor PTV was predictors of BCR according to population, however, the number of studies with large sample sizes was relatively fewer (4 for TV, 2 for PTV). Subsequent studies with large sample sizes should be conducted to further confirm the effects of TV and PTV on BCR.

Difference in valuation methods and sample sizes could be possible explanations for inconsistent results about the prognostic values of TV and PTV in previous studies, while another possible explanation was cohort selection. Manoharan et al. [35] reported that TV did not predict BCR in prostate cancer patients with Gleason score 8-10, and You et al. [34] demonstrated that PTV was not a significant predictor of BCR in men with pT3-4 prostate cancer. In our meta-analysis, most of the included studies did not selected patients based on clinicopathologic parameters, like Gleason score, pT stage. Besides, type of variables regarding TV and PTV were found to be different in different studies, which might explain the inconsistence of the results. In our meta-analysis, we only included studies that regarded TV and/or PTV as contin-

uous variables. However, there are studies that analyzed TV and PTV as categorical variables defined by different cut-off values [36-38]. Some studies showed that a TV cut-off of 0.5 ml might present an important role in the definition of insignificant prostate cancer [39-41] and when a TV cut-off of 0.5 ml was used, a significant association between TV and BCR after RP was found in previous studies [41, 42]. Although these studies showed significant results, we could not combine them to get a pooled result.

Several guidelines, including D'Amico risk-group classification and CAPRA score were used to define the risk groups of localized prostate cancer [43, 44]. As our study showed that both TV and PTV were predictors of BCR after RP, it seemed that they could be used to define the risk groups of localized prostate cancer, thereby directing the postoperative management (e.g. radiotherapy or hormone therapy). While, future studies are needed to determine the thresholds of TV and PTV.

Limitations of this meta-analysis should be noted. Firstly, random-effects model was used since between-study heterogeneity was found in the meta-analysis, which might affect the strength of the results in our study. We conducted sensitivity analyses while the results were considered stable. Moreover, we performed subgroup analyses to explore the source of heterogeneity, which showed that evaluation method might be the source of heterogeneity in the analysis of PTV, while we could not find the source of heterogeneity in the analysis on TV. Secondly, most of the included studies were retrospective studies, prospective studies with large sample sizes were needed to further confirm the prognostic values of TV and PTV.

In conclusion, our meta-analysis demonstrated that both TV and PTV had significant correlations with BCR after RP. Therefore, TV and PTV should be considered when assessing BCR risk in RP specimens.

Disclosure of conflict of interest

None.

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