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Review Article

Positive surgical margins after partial nephrectomy for renal cell carcinoma: a systematic review and meta-analysis

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Abstract: Purpose: To compare the outcomes of prognosis of positive surgical margins (PSM) and negative surgical margins (NSM) after partial nephrectomy (PN). We performed this study to assess local recurrence, distant recurrence and survival rates after PN. Materials and Methods: We searched PubMed, Web of science and the Cochrane Library. Three independent reviewers extracted data using a standardized form. Quality of the selected studies was assessed using the Newcastle-Ottawa Scale (NOS) for nonrandomized studies. Results: A total of 17 studies and 8156 patients were included. All studies were based on non-randomized, retrospective cohorts and the methodological quality varied. When analyzing recurrence rates, the PSM group had higher rates of local recurrence ($P < 0.00001$; RR: 4.83), distant recurrence ($P < 0.00001$; RR: 5.99) and overall recurrence ($P < 0.00001$; RR: 3.76). For survival analysis, the PSM group had a lower overall survival (OS) rate compared to the NSM group ($P = 0.03$; RR: 0.63). There was no significant difference between the two groups regarding the rate of cancer-specific survival (CSS) ($P = 0.40$; RR: 0.99). Conclusions: This meta-analysis showed that PSM after PN increases the risks of local and distant recurrences after PN. In addition, patients with PSM after PN had poorer OS. However, PSM did not appear to influence CSS. Active surveillance may not be recommended for patients with PSM after PN. To acquire more reliable outcomes of prognosis for patients with PSM after PN, large-scale clinical studies with long-term follow-up are needed.

Keywords: Renal cancer, partial nephrectomy, surgical margins, recurrence, survival, meta-analysis

Introduction

Renal cell cancer (RCC) represents 2-3% of all cancers. The estimated numbers of new cases and deaths were 61,560 and 14,080, respectively, in the United States in 2015 [1]. Despite a rapid increase in RCC incidence for several decades, incidence rates for RCC stabilized from 2007 to 2011, likely due to the increasing use of abdominal imaging tests in annual heath checks. Moreover, death rates due to RCC decreased by 0.9% annually from 2007 to 2011 [2]. Nevertheless, because of its relatively high prevalence, RCC has become an important healthcare issue worldwide. For localized RCC, curative surgical resection of the tumor is considered to be the first-line treatment. Partial nephrectomy (PN) and radical nephrectomy (RN) are the two major types of surgical resection. For localized tumors, of which the T staging is T1, PN is recommended [3, 4]. PN spares nephrons and may improve the prognosis after surgery. However, in some cases, PN may not confirm the complete resection of a tumor, thereby causing positive surgical margins (PSM), which will increase the risk of local recurrence, disease progression and lessen expected survival [5, 7, 8]. Several therapeutic options are available for patients with PSM, including immediate remedial RN, repeat-PN, energy ablation and active surveillance [6-8]. However, some studies have suggested that there is no correlation between PSM and poorer oncologic outcomes [9, 10]. Therefore, whether patients with PSM should receive further treatment remains controversial.

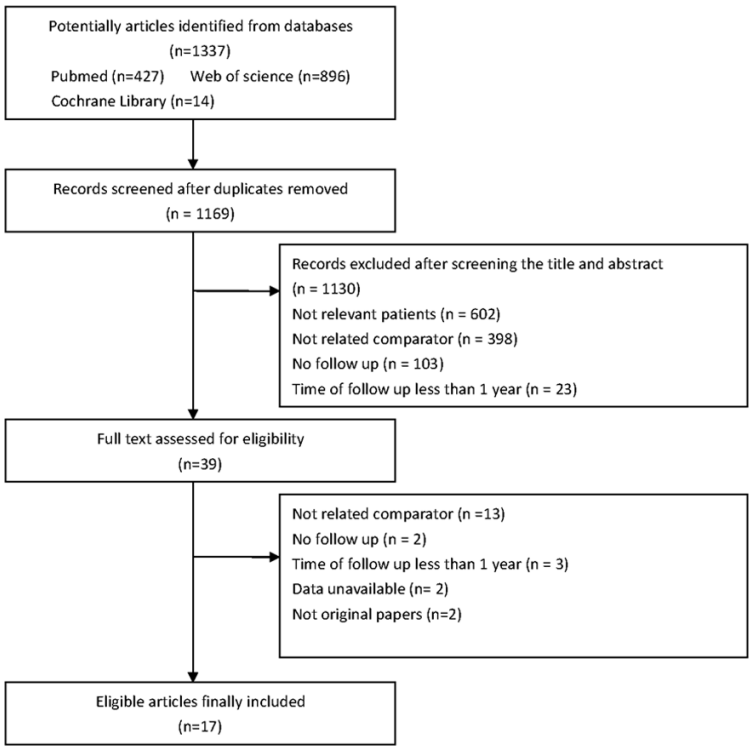


Figure 1. Flowchart of study selection process.

The objective of this study was to perform meta-analyses to evaluate the associations between oncologic outcomes (e.g. local recurrence, distant recurrence, overall survival (OS), and cancer-specific survival (CSS), etc.) and PSM after PN.

Materials and methods

Search strategy

We searched PubMed, Web of science and the Cochrane Library beginning Aug 01, 2015. We retrieved citations using combinations of the medical subject heading (MeSH) terms "kidney neoplasms", for MeSH search, and we also used the keywords "renal cancer", "RCC", "partial nephrectomy", "nephron sparing surgery", "PN", and "NSS" for freedom search. Every possible combination was taken into consideration.

Inclusion criteria and study eligibility

We defined study eligibility using the patient population, comparator, outcomes, and data integrities. The inclusion criteria were: (1) the manuscript focused on patients with renal malignancy tumors; (2) the oncologic outcomes of PSM and NSM after PN were compared; and (3) studies in which patients received active surveillance after being diagnosed with PSM. The exclusion criteria were (1) studies that did not focus on patients with renal malignancy tumors; (2) studies without follow-up, or a follow-up period less than 1 year; (3) patients did not receive active surveillance after being diagnosed with PSM; (4) data was not available for further analysis; (5) control groups were not NSM (non-relevant comparators); (6) the literature was not a research article (e.g. review articles, letters, commentaries, systematic research reviews, meta-analyses, etc.); and (7) full articles were not available.

Ultimately, 1337 potentially relevant articles were identified and 1298 were excluded by reviewing the titles and abstracts of each search result based on exclusion criteria. The remaining 39 articles with full texts were further evaluated. Among them, 22 articles were excluded because 13 articles included non-relevant comparators, data from two articles were unavailable, two articles did not report outcomes of follow-up, the follow-up periods of three articles were less than one year, and two articles were not research articles. Finally, 17 articles were included yielding 8156 patients. No duplication of study populations was found in the studies (**Figure 1**).

According to "The Oxford 2011 Levels of Evidence", all studies included were considered level 3 evidence [11]. The Newcastle-Ottawa Scale (NOS) for cohort studies was used to assess the quality of each study [12]. This scale contains eight items, categorized into three dimensions including selection, comparability, and outcome. A maximum of one star could be awarded for each item, while the item of comparability allows two stars. The total score ranges from 0 to 9 for the increasing quality of study. The assessment of the included studies is shown in **Table 2**. Three independent researchers performed the quality assessment and data extraction using a piloted form. The

Table 1. Demographics of included studies

Study (Year)	Scores of study Quality	Follow-up (month)	PSM						NSM					
			N (477)	Local	Distant	Total	Overall	Cancer-specific	N (7679)	Local	Distant	Total	Overall	Cancer-specific
Rahul (2014)	9	23.7	59	-	-	4	52	52	928	-	-	49	869	926
JimC (2014)	6	32.4	8	1	0	1	-	-	135	0	1	1	-	-
Ricardo (2013)	9	38	2	0	0	0	-	-	135	-	-	4	-	133
Kathleen (2013)	7	28.6	5	1	1	2	4	4	16	6	0	6	15	0
Ifeanyi (2013)	6	94.8	71	-	-	-	60	65	593	-	-	-	525	545
Ali (2013)	8	63.6	21	2	2	4	-	-	911	7	2	9	-	-
Andrea (2011)	6	51	26	1	-	-	-	-	1152	7	-	-	-	-
Bensalah (2010)	9	37	111	7	4	11	99	105	664	7	7	14	606	637
Yossepowi (2008)	8	39.6	77	2	4	6	-	-	1313	39	52	91	-	-
Desai (2008)	7	56.4	5	0	0	0	5	5	45	0	1	1	44	44
Kwon (2007)	8	22	57	2	2	4	-	-	713	4	10	14	-	-
Permp (2006)	7	25	7	0	1	1	-	6	502	-	-	70	-	-
Ray (2006)	7	24	8	0	2	2	-	-	68	3	0	3	-	-
Duvdevani (2005)	6	51	4	1	0	1	-	-	295	2	3	5	-	292
Zigeuner (2003)	7	80.5	6	2	3	3	-	-	108	7	11	14	-	-
Sutheland (2002)	9	49	3	1	1	1	-	-	41	1	0	1	-	-
Piper (2001)	7	60	7	0	2	2	6	6	60	1	2	2	60	60

PSM: positive surgical margin; NSM: negative surgical margin; Local: Local recurrence; Distant: Distant recurrence; Total: Total recurrence; Overall: Overall survival; Cancer-specific: Cancer-specific survival. The total score ranges from 0 to 9 for the increasing quality of study according to The Newcastle-Ottawa Scale.

data included the first author, publication year, country of origin, study setting, number of eligible patients, mean age, mean tumor size (when available), body mass index, oncologic outcomes and additional clinical data (for instance, histology, T stage and grade classification). Disagreements between the reviewers were resolved by discussion or in consultation with other specialists.

Data analysis

Meta-analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) and StataSE12.0 for power analysis calculations. The Cochrane Q statistic and quantified I^2 metrics were used to assess statistical heterogeneity. Relative risk (RR) and 95% confidence intervals (CI) were used for dichotomous variables. Heterogeneity was analyzed using a χ^2-test with n-1 degrees of freedom. A p value of 0.05 was used for statistical significance with the I^2 test. I^2 values of 25%, 50%, and 90% corresponded to low, moderate, and high levels of heterogeneity, respectively. Random-effects models were used if heterogeneity existed. To assess the risk of publication bias, we used a funnel plot when at least 10 statistically significant studies were included in the meta-analysis, and an asymmetrical plot suggested a possible publication bias [13].

Sensitivity analysis and meta-regression analysis

Sensitivity analysis was performed by reanalyzing the data using different statistical approaches (e.g. using a fixed effects model instead of a random effect model, using different effect measures (relative risk, odds ratio, risk difference)) and by funnel plots to evaluate publication bias [14]. We also used meta-regression analysis to evaluate any associations between oncologic outcomes (odds ratio of progression) and factors (PSM, time of follow-up) if the heterogeneity between the studies was too high (I^2>50%). The method used to estimate the between-study variance was the restricted maximum-likelihood (REML).

Results

The characteristics of the included study populations are showed in **Table 1**. All studies were based on non-randomized, retrospective cohorts. Among the 17 research articles, 13 were included in the current meta-analysis for evaluating local recurrence of the tumor [7-10, 15-23], 12 for evaluating distant recurrence

Table 2. Assessment of Quality of Studies

Author (Year)	Selection	Comparability	Outcome	Score
Ali (2013)	★★★★	★★	★★★	★★★★★★★★★
Andrea (2011)	★★★	★	★★	★★★★★★
Bensalah (2010)	★★★★	★★	★★★	★★★★★★★★★
Desai (2008)	★★★	★	★★★	★★★★★★★
Duvdevani (2005)	★★★	★	★★	★★★★★★
Ifeanyi (2013)	★★★★	★★	★★	★★★★★★★★
JimC (2014)	★★★	★	★★	★★★★★★
Kathleen (2013)	★★★★	★★	★★★	★★★★★★★★★
Kwon (2007)	★★★★	★★	★★	★★★★★★★★
PermpKosol (2006)	★★★★	★	★★	★★★★★★★
Piper (2001)	★★★★	★★	★★★	★★★★★★★★★
Rahul (2014)	★★★★	★★	★★★	★★★★★★★★★
Ray (2006)	★★★★	★	★★	★★★★★★★
Ricardo (2013)	★★★★	★	★★	★★★★★★
Sutheland (2002)	★★★★	★	★★	★★★★★★★
Yossepowich (2008)	★★★★	★★	★★★	★★★★★★★★★
Zigeuner (2003)	★★★★	★	★★	★★★★★★★

[7-10, 15, 17, 23], 15 for evaluating total recurrence [7-10, 15, 17-26], and 6 for analyzing overall survival and cancer-specific survival [9, 17, 18, 23, 24, 27]. A total of 8156 patients were included. The median follow-up time was 39.9 months (22 to 94.8). Four hundred seventy-seven (477) patients had PSM after surgery, and all received active surveillance thereafter. For the entire population, the local recurrence rate was 1.8% (PSM 5.9% vs. NSM 1.5%), distant recurrence rate was 1.9% (PSM 7.1% vs. NSM 1.6%), total recurrence rate was 5.2% (PSM 11.1% vs. NSM 4.8%), OS rate was 91.5% (PSM 87.6% vs. NSM 91.9%) and CSS rate was 95.5% (PSM 94.6% vs. NSM 96.6%).

Meta-analysis for outcomes

Table 1 and **Figure 3** show the oncologic outcomes of patients with PSM and NSM after PN. When analyzing the recurrence rates, the PSM group had a higher rate of local recurrence ($P < 0.00001$; RR: 4.83; 95% CI, 2.35-9.91) (**Figure 2A**), distant recurrence ($P < 0.00001$; RR: 5.99; 95% CI, 2.99-11.83) (**Figure 2B**) and total recurrence ($P < 0.00001$; RR: 3.76; 95% CI, 2.18-6.49) (**Figure 2C**). For survival analysis, the PSM group had a lower OS rate compared to the NSM group ($P = 0.03$; RR: 0.63; 95% CI, 0.42-0.95) (**Figure 2D**). There was no significant difference between the two groups regarding the rate of CSS ($P = 0.40$; RR: 0.99; 95% CI, 0.97-1.01) (**Figure 2E**).

There was moderate heterogeneity in local recurrence ($I^2 = 45\%$, $P = 0.05$) and distant recurrence ($I^2 = 43\%$, $P = 0.06$). High heterogeneity was observed in total recurrence ($I^2 = 57\%$, $P = 0.003$). There was no heterogeneity of OS between studies ($I^2 = 0\%$, $P = 0.91$) and CSS ($I^2 = 0\%$, $P = 0.7$). The funnel plot did not show significant asymmetry for local recurrence (Egger test $P = 0.684$) (**Figure 3A**) or total recurrence (Egger test $P = 0.202$) (**Figure 3C**). However, asymmetry was observed in the analysis of distant recurrence (Egger test $P = 0.011$) (**Figure 3B**).

Heterogeneity and sensitivity analysis

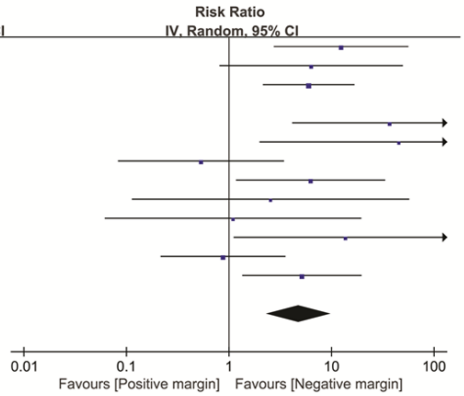
High heterogeneity was observed in total recurrence ($I^2 = 57\%$, $P = 0.003$). Subgroup analysis was not possible due to lack of data, so the meta-regression analysis of a single covariate (follow-up time) was conducted. Tau^2 value decreased from 0.6294 to 0.3646 after meta-regression analysis; this means that the difference between follow-up times could explain 42.1% ((0.6294-0.3646)/0.6294) of the heterogeneity.

In sensitivity analyses, we did not identify any significant differences in the effect measures

A

Study or Subgroup	Positive margin Events	Total	Negative margin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ali 2013	2	21	7	911	10.7%	12.39 [2.74, 56.15]
Andrea 2011	1	26	7	1152	7.6%	6.33 [0.81, 49.61]
Bensalah 2010	7	111	7	664	14.3%	5.98 [2.14, 16.73]
Desai 2008	0	5	0	45		Not estimable
Duvdevani 2005	1	4	2	295	7.0%	36.88 [4.13, 328.94]
JimC 2014	1	8	0	135	4.2%	45.33 [1.98, 1035.62]
Kathleen 2013	1	5	6	16	8.6%	0.53 [0.08, 3.44]
Kwon 2007	2	57	4	713	9.6%	6.25 [1.17, 33.42]
Piper 2001	0	7	1	60	4.2%	2.54 [0.11, 57.25]
Ray 2006	0	8	3	68	4.8%	1.10 [0.06, 19.52]
Sutheland 2002	1	3	1	41	5.8%	13.67 [1.11, 168.46]
Yossepowich 2008	2	77	39	1313	11.4%	0.87 [0.22, 3.55]
Zigeuner 2003	2	6	7	108	11.9%	5.14 [1.35, 19.63]
Total (95% CI)		**338**		**5521**	**100.0%**	**4.83 [2.35, 9.91]**
Total events	20		84			

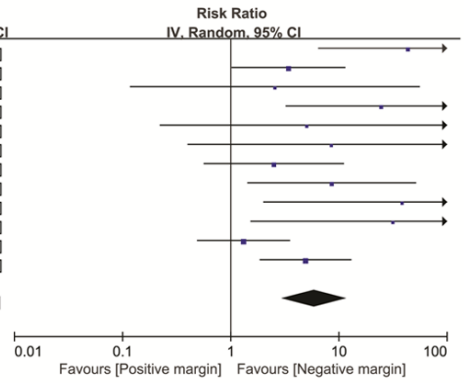
Heterogeneity: Tau² = 0.67; Chi² = 20.01, df = 11 (P = 0.05); I² = 45%
Test for overall effect: Z = 4.29 (P < 0.0001)



B

Study or Subgroup	Positive margin Events	Total	Negative margin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ali 2013	2	21	2	911	8.2%	43.38 [6.41, 293.43]
Bensalah 2010	4	111	7	664	13.2%	3.42 [1.02, 11.49]
Desai 2008	0	5	1	45	4.1%	2.56 [0.12, 55.91]
Duvdevani 2005	1	4	3	295	7.5%	24.58 [3.21, 188.46]
JimC 2014	0	8	1	135	4.0%	5.04 [0.22, 115.07]
Kathleen 2013	1	5	0	16	4.1%	8.50 [0.40, 181.70]
Kwon 2007	2	57	10	713	10.9%	2.50 [0.56, 11.15]
Piper 2001	2	7	2	60	8.8%	8.57 [1.42, 51.69]
Ray 2006	2	8	0	68	4.4%	38.33 [1.99, 736.69]
Sutheland 2002	1	3	0	41	4.2%	31.50 [1.52, 653.16]
Yossepowich 2008	4	77	52	1313	15.3%	1.31 [0.49, 3.53]
Zigeuner 2003	3	6	11	108	15.4%	4.91 [1.85, 13.04]
Total (95% CI)		**312**		**4369**	**100.0%**	**5.95 [2.99, 11.83]**
Total events	22		89			

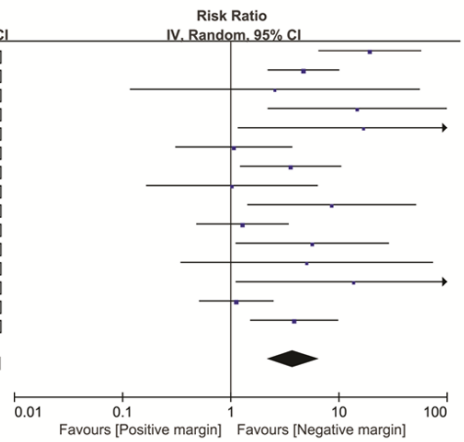
Heterogeneity: Tau² = 0.55; Chi² = 19.22, df = 11 (P = 0.06); I² = 43%
Test for overall effect: Z = 5.08 (P < 0.00001)



C

Study or Subgroup	Positive margin Events	Total	Negative margin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ali 2013	4	21	9	911	8.7%	19.28 [6.45, 57.66]
Bensalah 2010	11	111	14	664	10.7%	4.70 [2.19, 10.09]
Desai 2008	0	5	1	45	2.5%	2.56 [0.12, 55.91]
Duvdevani 2005	1	4	5	295	5.1%	14.75 [2.19, 99.30]
JimC 2014	1	8	1	135	3.2%	16.88 [1.16, 245.75]
Kathleen 2013	2	5	6	16	7.9%	1.07 [0.31, 3.71]
Kwon 2007	4	57	14	713	8.8%	3.57 [1.22, 10.50]
Permp Kosol 2006	1	7	70	502	5.4%	1.02 [0.16, 6.37]
Piper 2001	2	7	2	60	5.5%	8.57 [1.42, 51.69]
Rahul 2014	4	59	49	928	9.4%	1.28 [0.48, 3.44]
Ray 2006	2	8	3	68	6.1%	5.67 [1.11, 28.99]
Ricardo 2013	0	2	4	135	3.2%	5.04 [0.34, 74.09]
Sutheland 2002	1	3	1	41	3.5%	13.67 [1.11, 168.46]
Yossepowich 2008	6	77	91	1313	10.5%	1.12 [0.51, 2.49]
Zigeuner 2003	3	6	14	108	9.6%	3.86 [1.51, 9.85]
Total (95% CI)		**380**		**5934**	**100.0%**	**3.76 [2.18, 6.49]**
Total events	42		284			

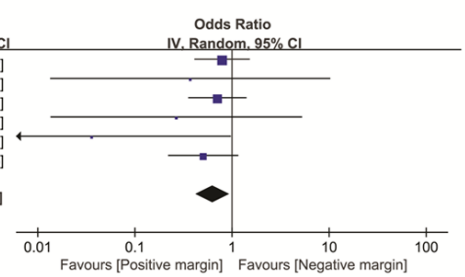
Heterogeneity: Tau² = 0.58; Chi² = 32.91, df = 14 (P = 0.003); I² = 57%
Test for overall effect: Z = 4.76 (P < 0.00001)



D

Study or Subgroup	Positive margin Events	Total	Negative margin Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Bensalah 2010	99	111	606	664	37.7%	0.79 [0.41, 1.52]
Desai 2008	5	5	44	45	1.5%	0.37 [0.01, 10.27]
Ifeanyi 2013	60	71	525	593	34.1%	0.71 [0.35, 1.41]
Kathleen 2013	4	5	15	16	1.8%	0.27 [0.01, 5.27]
Piper 2001	6	7	60	60	1.5%	0.04 [0.00, 0.97]
Rahul 2014	52	59	869	928	23.5%	0.50 [0.22, 1.16]
Total (95% CI)		**258**		**2306**	**100.0%**	**0.63 [0.42, 0.95]**
Total events	226		2119			

Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 5 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)



E

Study or Subgroup	Positive margin Events	Total	Negative margin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bensalah 2010	105	111	637	664	18.1%	0.99 [0.94, 1.03]
Desai 2008	5	5	44	45	0.7%	0.95 [0.74, 1.21]
Ifeanyi 2013	65	71	545	593	7.2%	1.00 [0.92, 1.07]
Kathleen 2013	4	5	16	16	0.2%	0.77 [0.48, 1.24]
Piper 2001	6	7	60	60	0.4%	0.82 [0.59, 1.14]
Rahul 2014	59	59	926	928	73.4%	0.99 [0.97, 1.02]
Total (95% CI)		**258**		**2306**	**100.0%**	**0.99 [0.97, 1.01]**
Total events	244		2228			

Heterogeneity: Tau² = 0.00; Chi² = 2.60, df = 5 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)

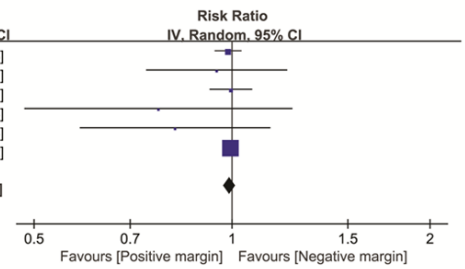


Figure 2. A: It is the forest plot that meta-analyzes the studies on local recurrence after PN. B: It is the forest plot that meta-analyzes the studies on distant recurrence after PN. C: It is the forest plot that meta-analyzes the studies on local and distant recurrence after PN. D: It is the forest plot that meta-analyzes the studies on Overall survival after PN. E: It is the forest plot that meta-analyzes the studies on Cancer-specific Survival after PN.

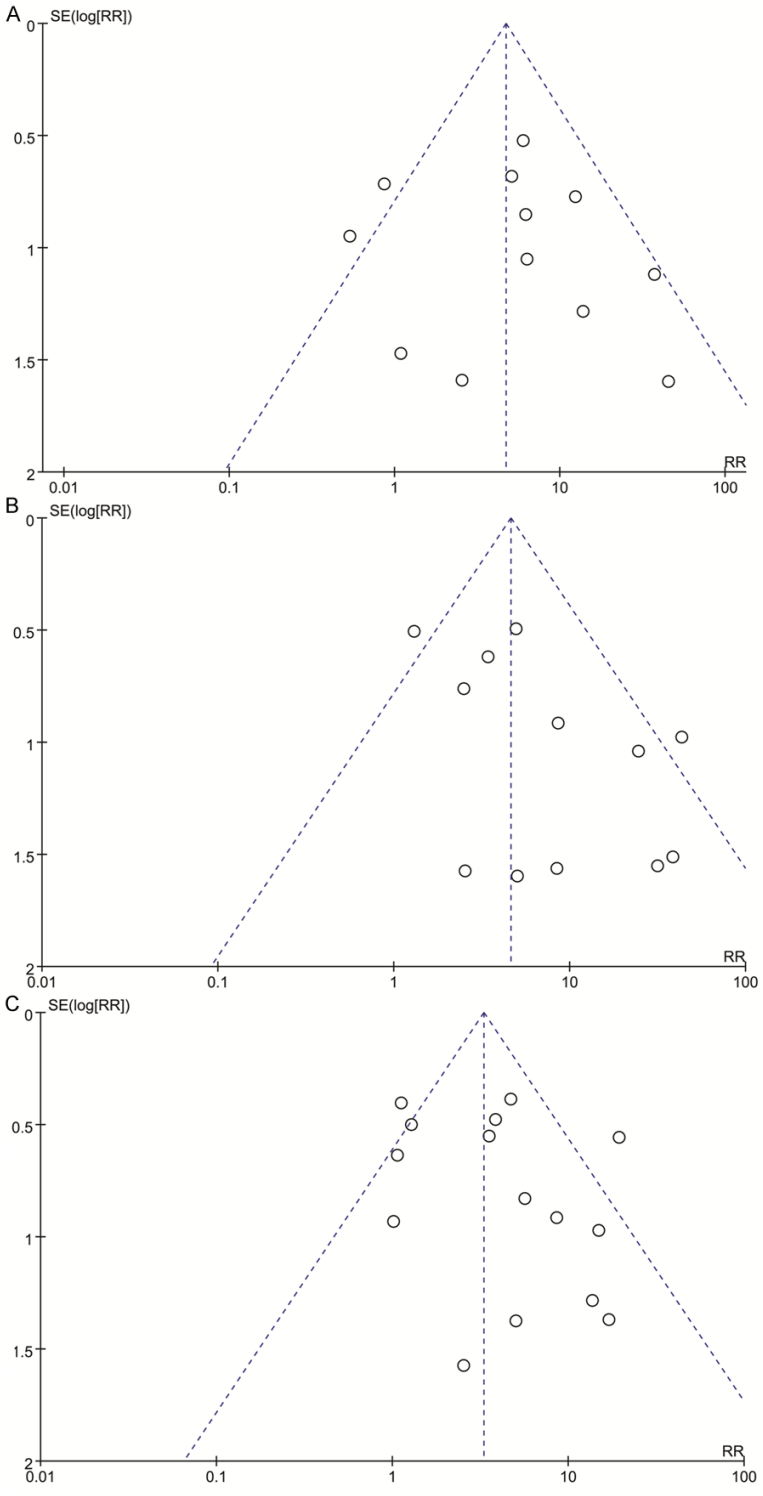


Figure 3. A: It is the funnel plot of the included studies which relate to local recurrence after PN. B: It is the funnel plot of the included studies which relate to distant recurrence after PN. C: It is the funnel plot of the included studies which relate to local and distant recurrence after PN.

(relative risk, odds ratio, risk difference) or heterogeneity using both random and fixed effect models (**Table 3**). Influence analysis showed that when excluding studies of lower quality (< 7 stars) for distant recurrence, the relative risk and heterogeneity for prognosis remained unchanged (RR of 5.31, 95% CI of 2.55 to 11.05, with heterogeneity of 45% I^2 and *P* value of 0.06). Consequently, we concluded that there were limited publication biases in the group of the distant recurrence, and the outcomes of meta-analysis were credible.

Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the prognosis of PSM and NSM after PN. The results of the meta-analysis of 8156 patients showed that PSM after PN (1) significantly increased the risk of local recurrence, distant recurrence and total recurrence and (2) significantly decreased the rate of OS, but (3) had no correlation with CSS. This result was synthesized from the data of previous studies, and this is the first time this result has been shown from a meta-analysis.

Though we anticipated that PSM after PN would increase the risk of local and distant recurrence, PSM was not significantly associated with CSS rates. This was probably because of the relatively low incidence of PSM: (1) the occurrence of the event (cancer-specific mortality (CSM) rate) was low due to the small

Table 3. Sensitive Analysis

A. Sensitive Analysis for the studies of local recurrence		
Analysis Model	Effect Measure	*P*-value
Fixed effect	OR: 5.04 (2.90, 8.75)	<0.00001
	RR: 4.68 (2.84, 7.71)	<0.00001
	RD: 0.02 (0.00, 0.05)	0.03
Random effects	OR: 5.24 (2.43, 11.29)	<0.00001
	RR: 4.83 (2.35, 9.91)	<0.00001
	RD: 0.02 (0.00, 0.05)	0.03
B. Sensitive Analysis for the studies of distant recurrence		
Analysis Model	Effect Measure	*P*-value
Fixed effect	OR: 4.92 (2.86, 8.47)	<0.00001
	RR: 4.59 (2.87, 7.33)	<0.00001
	RD: 0.03 (0.00, 0.05)	0.02
Random effects	OR: 7.08 (3.20, 15.69)	<0.00001
	RR: 5.99 (2.99, 11.83)	<0.00001
	RD: 0.03 (0.00, 0.06)	0.03
C. Sensitive Analysis for the studies of total recurrence		
Analysis Model	Effect Measure	*P*-value
Fixed effect	OR: 3.61 (2.47, 5.27)	<0.00001
	RR: 3.29 (2.38, 4.54)	<0.00001
	RD: 0.05 (0.02, 0.08)	0.0008
Random effects	OR: 4.33 (2.35, 7.97)	<0.00001
	RR: 3.76 (2.18, 6.49)	<0.00001
	RD: 0.05 (0.02, 0.08)	0.0008

sample of PSM patients, thus, the CSM could not truly represent the actual mortality rate of patients with PSM; (2) the difference of CSM rates between the PSM group and the NSM group did not reach a statistically significant level. However, since PSM was a risk factor for poor OS, we still suggest that patients with a PSM diagnosis after PN should receive further intervention instead of active surveillance.

Possible interventional therapeutic options for patients with PSM include remedial RN, repeated PN and energy ablation [28]. Results from a retrospective study [29] showed that there was no residual tumor in patients who received delayed RN after being diagnosed with PSM. Disease progression or CSM in patients treated with RN was also not observed after a median follow-up of 71 months. RN would sacrifice normal nephrons, which has the potential to increase the risk of long term kidney dysfunction and, ultimately, the risk of cardiovascular events [30]. Thus, to preserve the nephron, repeat PN seems to be a better choice. Moreover, it should be noted that residual tumors were rarely found in the repeat PN tissues [31]. Energy ablation of the tumor bed (radiofrequency or cryotherapy) is a minimally invasive treatment option; however, no specimen was available from this procedure for pathological confirmation, and the tissue alterations could interfere with imaging test during follow-up [6]. Moreover, a study revealed that PSM in aggressive, high-grade tumors had a greater risk of poor prognosis [32]. The treatment choices for PSM after PN were still under discussion, as it was necessary to comprehensively evaluate the status of the patients and the surgeons' skills before making the decision.

Due to the existence of high heterogeneity between studies in total recurrence, we performed meta-regression analysis adjusting for the covariant of follow-up time, and tried to explain the heterogeneity. Because the occurrence rate of PSM is low, the sensitivity and influence analysis were conducted so as to evaluate the publication bias.

There are still some limitations in this meta-analysis study. (1) The occurrence of PSM is low and, thus, the sample size of the PSM group is relatively small. This also caused moderate to high heterogeneity in the current study. However, by using meta-regression analysis, we successfully lowered the heterogeneity by 42.1%. (2) All the studies are retrospective, and the evidence level of each study is moderate. However, randomized prospective clinical trials will not be appropriate in this kind of studies due to ethical issues. (3) A difference in rates of CSS among the PSM and NSM groups was not observed, likely due to the time span of follow-up for each study not being long enough. (4) The difference of follow-up time affects the heterogeneity between studies. (5) There are not enough relevant data of pathological T stage and grade, so we cannot evaluate the correlation between PSM and pathological T stage or grade.

Conclusion

In conclusion, PSM after PN will increase the risk of local and distant recurrences after PN. In addition, patients with PSM after PN had

poorer OS. However, PSM did not significantly influence CSS. Active surveillance may not be recommended for patients with PSM after PN. To acquire more reliable outcomes of prognosis for patients with PSM after PN, large-scale clinical studies with long-term follow-up are needed.

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Disclosure of conflict of interest

None.

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