Impact of Positive Surgical Margins on Recurrence and Overall Survival Following Partial Nephrectomy: A Systematic Review and Meta-Analysis

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Purpose: Positive surgical margins (PSM) following partial nephrectomy (PN) for renal cell carcinoma (RCC) are a concern due to potential implications for recurrence and survival. This systematic review and meta-analysis assess the impact of PSM on recurrence rates and progression-free survival in RCC patients.

Methods: We conducted a systematic search of PubMed, Embase, Scopus, Cochrane, and Web of Science databases from inception through July 2024. Studies examining recurrence and survival outcomes in RCC patients with and without PSM post-PN were included. A random-effects model was applied to calculate pooled hazard ratios (HR) and 95% confidence intervals (CI) for recurrence and survival.

Results: Thirty studies met the inclusion criteria. Our analysis showed that PSM was significantly associated with a higher risk of local recurrence (HR = 2.13, 95% CI: 1.67–2.72) and a lower recurrence/progression-free survival (HR = 1.70, 95% CI: 1.40–2.07) compared to negative surgical margins. Subgroup analyses indicated consistent results across study designs and RCC histologic subtypes.

Conclusion: The presence of PSM following PN for RCC is associated with a 2.13-fold increase in local recurrence and a 1.7-fold reduction in progression-free survival, emphasizing the need for precise margin management during surgery. These findings highlight the importance of optimizing surgical techniques and considering adjuvant treatment strategies for patients with PSM to improve oncologic outcomes.

Keywords: renal cell carcinoma; partial nephrectomy; positive surgical margins; recurrence; progression-free survival; meta-analysis

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common forms of kidney cancer, accounting for the majority of malignancies originating in the kidney[(1)]. With the increasing use of imaging technologies, early detection of small renal masses has become more frequent, leading to shifts in management strategies toward organ-sparing procedures[(2)]. Partial nephrectomy (PN), which removes only the tumor and spares the remaining kidney tissue, has become a standard approach for treating localized RCC, especially for tumors confined to the kidney and in patients with predisposing risk factors for renal impairment. By preserving renal function, PN can reduce the risk of chronic kidney disease, potentially lowering the overall morbidity and mortality associated with radical nephrectomy[(3,4)].

Despite these benefits, partial nephrectomy introduces specific challenges, notably the risk of positive surgical margins (PSM). A positive margin indicates that cancerous cells remain at the edge of the excised tissue, suggesting incomplete tumor resection[(5)]. The implications of PSM are critical in the context of RCC, as they may serve as a harbinger of local recurrence, tumor progression, or even metastasis, thus impacting survival outcomes. Consequently, the management of PSM in RCC patients following PN has become an area of intense clinical interest and ongoing debate[(6,7)].

The presence of PSM raises several clinical questions, primarily regarding the likelihood of cancer recurrence and its influence on overall survival[(8,9)]. In some cases, PSM may indicate a biologically more aggressive tumor phenotype, thereby increasing the risk of adverse oncological outcomes. However, not all patients with PSM experience recurrence, suggesting that factors such as tumor grade, stage, and patient characteristics may modulate the risk associated with positive margins. The clinical relevance of PSM remains a topic of substantial variability, with some studies identifying a significant association between PSM and poorer outcomes, while others report minimal or no impact on survival and recurrence rates[(10,11)].

As RCC treatment guidelines increasingly emphasize personalized medicine, understanding the precise implications of PSM is essential for guiding treatment plans, determining follow-up intervals, and deciding on the necessity of adjuvant therapy. For clinicians, this information is particularly valuable in counseling patients about the risks and potential outcomes associated with partial nephrectomy, especially in comparison to radical procedures[(12,13)].

To date, numerous studies have explored the relationship between PSM and RCC outcomes, yet results have been inconsistent[(14,15)]. Variability in patient populations, surgical techniques, definitions of PSM, follow-up durations, and outcome measures complicate

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Table 1. Baseline characteristics of included studies

First Author (Year)	sample size	Tumor T stage	Positive. Margin	Negative. Margin	Age	BMI	tumor size	RENAL score	Surgery type	Pathologic subtype(number)	Time to follow-up (Months)	Total Quality Score
Taneja 2024	88	T3a:66, T3b:8, T3c:1, T3 undefined:13	7	81	64.0	NR	7.1	NR	Open radical nephrectomy, Laparoscopic radical nephrectomy, Open partial nephrectomy	Clear cell RCC:74, Chromophobe RCC:4, Papillary RCC (type 2):3, Other:7	58	9
Sarkis 2024	3451	T1a:1787; T1b:572; T2a:60; T2b: 15, T3a:356; T3b:3; T3c:1, T4:2	202	2818	63.0	NR	3.2	7	Robot-assisted Partial Nephrectomy	Clear cell RCC:1954, Papillary RCC:464, Chromophobe RCC:288, Oncocytoma:305	6	8
Mari 2024	1611	T1a:1190, T1b:496, T2:31, T3a:117	109	1508	62.6	26.9	NR	8	robot-assisted partial nephrectomy	Clear cell RCC:1134, Papillary RCC:314, Chromophobe RCC:148, Unclassified RCC:2	23	7
Hulin 2024	1106	T1a:954, T2:34, T3:119	61	1054	66.0	27	38	8	Laparoscopic, Robotic, Open	Clear cell:830, Papillary:176, Chromophobe:109	51	9
Morrone 2022	2066	T1a:1394, T1b: 668, T2a:14	136	2030	60.17	27.57	3.60	NR	Laparoscopic, Robotic, Open	NR	19	9
Wahba 2021	943	1a 317 1b 46 2a, 2b, 3a 10 Missing 1	21	922	57.7	NR	3.1	7.6	robot-assisted partial nephrectomy	Clear cell 278 Papillary 64 Other 32	77.7	6
Radfar 2021	122	NR	37	80	58.4	NR	NR	NR	NR	Clear cell:80, Papillary:18, Chromophobe:24	33	7
Takagi 2020	1227	T1a:970, T1b:237, pT3:20	19	1208	59.0	24	30	NR	Laparoscopic, Robotic, Open	NR	45	7
Rothberg 2019	432	T1a:325, T1b:54 , T2a:3,T3a:16	29	403	61.1	29.5	3.1	7	robot-assisted partial nephrectomy	Clear cell:298, Papillary:89, Chromophobe:30, Other:15	45.1	8
Rothberg 2020	836	T1a:619, T1b: 204, T2a:16	41	795	61.0	30.5	3	7	Robot-Assisted Partial Nephrectomy	Clear cell RCC:530, Papillary RCC:158, Chromophobe RCC:53	13.1	6
Carvalho 2020	424	T1a:287, T1b: 112,T2a: 7;T3a:17,T3b: 1	16	408	61.8	NR	4	7.5	Laparoscopic, Robotic, Open	Clear cell RCC: 169; Chromophobe RCC: 69; Papillary RCC:68; Angiomyolipoma: 41; Oncocytoma: 35; Others:42	23	7
Çakıcı 2020	302	T1a:185, T1b:105, T2a:8, T2b:3, T3a:1	38	264	58.1	28.1	38.6	6.8	Open, laparoscopically	Clear cell:216, Papillary:53, Chromophobe:28, Other:5	85.2	7
Kızılay 2019	125	NR	6	119	54.7	22.7	31.12 mm	NR	Laparoscopic, Robotic, Open	Clear cell RCC:83, Chromophobe cell RCC:13, Papillary-type RCC:24,	55.35	7
BeKSac 2018	1298	T1a:993, pT1b:220, pT2a: 10, pT2b: 1, pT3a:74	156	1142	55.8	30.8	3.1	6.9	Open, laparoscopically	NR	27.3	9

Petros 2018	1863	pT1a:23, pT1b:4, pT3a:7	57	1806	59.0	31	3.2	8	Open, laparoscopically	Clear cell:21, Papillary:9, Chromophobe:2, Unclassified:2	62	8
Marchiñena 2018	314	pT1a:19, pT1b:3, pT3a:7	22	292	58.9	28.6	27mm	NR	Open, Minimally Invasive	Clear-cell:245, Chromophobe:45, Papillary type I:10, Papillary type II:10	24	6
Li 2018	600	T1a:	20	580	NR	NR	3	NR	Open, Minimally Invasive	Clear cell cancer: 16 Papillary cell cancer:1 Chromophobe: 3	56	7
Tellini 2019	459	pT1a:370, pT1b:64, pT2:7, pT3a:18	27	432	62.2	NR	3.1	NR	open retroperitoneal, laparoscopic, or robot assisted approaches	Clear cell:337, Papillary: 79, Chromophobe: 31, Others:12	43	7
Bansal 2017	1103	T1 879 /T2 34 /T3 66	71	972	61.0	NR	3	7	Laparoscopic, Robotic, Open	Clear-cell:686, Chromophobe:71, Papillary type I:191,other:75,Unclassified:20	15	8
Mouracade 2017	830	T1:721, T2:13, T3:96	59	771	61.0	29.5	3.1	7.5	Open/ Robotic	NR	20	9
Minervini 2017	1055	T1a:820, T1b: 199; ct2:36	96	959	59	NR	NR	NR	Laparoscopic, Robotic, Open	NR	24	6
Jin Oh 2016	702	T1a 690/T3a 12	7	695	54.8 8	24.55	23.05	NR	Open/ Robotic	NR	20	8
Maurice 2016	6038	T1 5773 /T2 125 /T3a 140	302	5736	58	NR	2.5	NR	All	Clear cell:2044, Papillary 935, Chromophobe: 368, Others 2691	71	9
Kang 2016	1831	T1a 1581, T1b 139	31	1782	55.8	24.7	24.7mm	NR	Open/ Robotic	NR	32.5	9
Bigot 2014	168	T2a 92, T2b 15, T3a:15	14	154	59.0	25	8	NR	open 154, Laparoscopic 11, Robotic 3	Malignant tumor 126, Clear-cell 74, Papillary 34, Chromophobe 12, Angiosarcoma 1, Mixed epithelial and stromal tumor 1, Sarcomatoid renal cell carcinoma 1, Mixed clear-cell and papillary 1, Renal cell carcinoma, unclassified 2	30	7
Khalifeh 2013	16,	T1a 763, T1b 107, T2a 15, T2b 1, T3a 45	21	922	59.0	30.1	4	7.1	Robotic	Clear cell 578, mixed 29, Papillary 223, Chromophobe 81, Unclassified 21, Other 11	63.6	6
Ani 2013	658	pT1a 524, pT1b 70, pT2 21, pT3a 46, pT3b 3	71	587	56.3	NR	6.5	6.5	open or laparoscopic	NR	7.9 years	8
Saito 2011	1373	NR	26	1347	59.8	24	2.26	NR	Open partial nephrectomy, Open nephrectomy, Laparoscopic nephrectomy	NR	26 months	8
Haferkamp 2010	168	T1 135, T2 15, T3 16, T4b 2	13	155	62.0	NR	6	NR	open or laparoscopic	Clear-cell RCC 147, Papillary 11, Chromophobe 4, Sarcomatoid 3, Mixed 3	99 months	7
Yossepowitch 2007	1344	T1a 1045, T1b 237, T2 27, T3 79	77	1313	63.0	25.5	3.2	NR	Partial Nephrectomy	Clear cell 880, Papillary 343, Chromophobe 130	3.4 years	

NR: Not reported

NR: Not reported

Table 2. The quality of cohort studies by using the Newcastle-Ottawa Scale

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	outcome of interest was not present at start of study	Adjustment for main confounding factor	controls for any additional factor	Assessment of outcome	follow-up long enough	Adequacy of follow up of cohorts	total
Taneja 2024	*	*	*	*	*	*	*	*	*	9
Sarkis 2024	*	*	*	*	*	*	*	*		8
Mari 2024	*	*	*	*	*	*	*			7
Hulin 2024	*	*	*	*	*	*	*	*	*	9
Morrone 2022	*	*	*	*	*	*	*	*	*	9
Wahba 2021	*		*	*		*		*	*	6
Radfar 2021	*	*	*	*	*			*	*	7
Takagi 2020	*	*	*	*			*	*	*	7
Rothberg 2019	*	*		*	*	*	*	*	*	8
Rothberg 2020	*			*	*		*	*	*	6
Carvalho 2020	*	*	*	*			*	*	*	7
Çakıcı 2020	*	*	*	*	*	*	*	*	*	9
Kızılay 7 2019	*	*			*	*		*	*	*
BeKSac 2018	*	*	*	*	*	*	*	*	*	9
Petros 2018	*	*	*	*	*		*	*	*	8
Marchi-ñena 2018	*		*	*			*	*	*	6
Li 2018	*	*	*		*	*	*		*	7
Tellini 2019	*	*	*			*	*	*	*	7
Bansal 2017	*		*	*	*	*	*	*	*	8
Moura-cade 2017	*	*	*	*	*	*	*	*	*	9
Minervini 2017		*			*	*	*	*	*	6
Jin Oh 2016	*	*		*	*	*	*	*	*	8
Maurice 2016	*	*	*	*	*	*	*	*	*	9
Kang 2016	*	*	*	*	*	*	*	*	*	9
Bigot 2014	*	*		*	*	*		*	*	7
Khalifeh 2013	*		*	*	*			*	*	6
Ani 2013	*	*	*	*		*	*	*	*	8
Saito 2011	*		*	*	*	*	*	*	*	8
Haferkamp 2010	*	*		*	*	*		*	*	7
Yossepo-witch2007	*	*	*	*	*	*	*	*	*	9

the establishment of clear clinical guidelines[16]. While some research emphasizes a strong correlation between PSM and higher recurrence rates, other studies fail to discover substantial differences in overall survival or recurrence-free survival. These discrepancies underscore the need for a comprehensive synthesis of existing evidence[17,18].

This systematic review and meta-analysis aim to clarify the prognostic implications of positive surgical margins in patients who have undergone partial nephrectomy.

METHODS

The study methodology adhered to the systematic review guidelines outlined in the Cochrane Handbook, with findings documented in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and

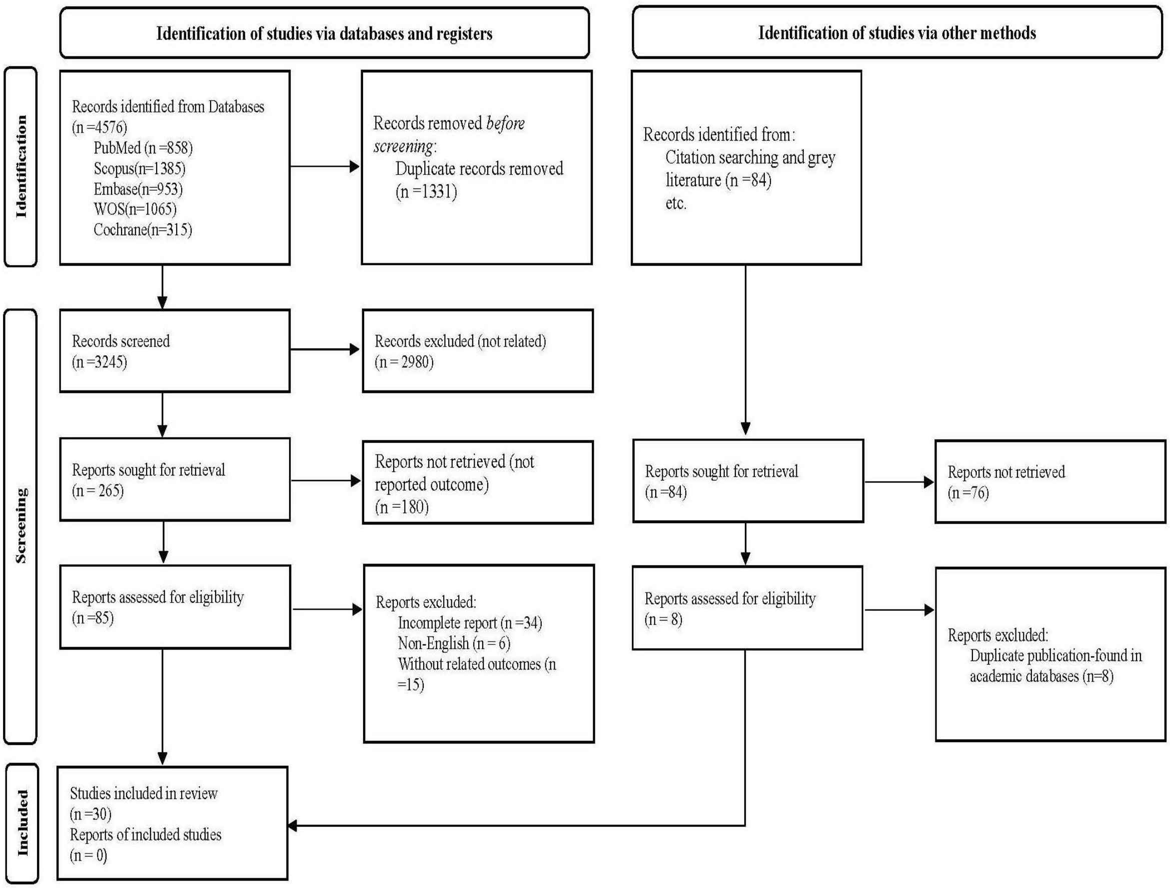

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (2020) of search process

Meta-Analyses (PRISMA) standards. The protocol for this systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024573929).

Information sources and search strategy

The systematic search process of this study was conducted in main databases including PubMed, Scopus, Web of Science, Embase and Cochrane Central Register of Controlled Trials. A thorough search was conducted across databases from their inception through to July 22, 2024. No limitations were imposed regarding language or publication status. The search strategy that used in the search process included : (("Kidney Neoplasms"[MeSH Terms] OR "Renal Cell Carcinoma" OR "Kidney Cancer" OR "Renal Cancer")) AND (("Partial Nephrectomy"[MeSH Terms] OR "Partial Nephrectomy" OR "Nephron-Sparing Surgery" OR "Kidney-Sparing Surgery")) AND (("Positive Surgical Margins" OR "Surgical Margins" OR "Incomplete Resection" OR "Margin Status")) AND (("Recurrence"[MeSH Terms] OR "Recurrence-Free Survival" OR "Progression-Free Survival" OR "Overall Survival" OR "Metastasis-Free Survival")). The details of the search strategy used in each of the databases are explained in the supplementary file 1. Boolean operators and specific database filters were strategically utilized to refine and enhance the search process. The search strategies were peer-reviewed by a second author (MAO) before implementation, following the Peer Review of Electronic Search Strategies (PRESS) Checklist. The reference lists of pertinent reviews and included studies were examined to identify additional relevant references. Finally, we searched Google Scholar to find more studies.

Eligibility criteria

In the present study we included observational studies (cross-sectional, case-control and cohort studies) that evaluated the presence of the positive margin status and its correlation with disease recurrence and survival among the adult patients (more than 18 years old) who undergo a robotic, laparoscopic, or open partial nephrectomy. We excluded other type of the studies including review studies, case reports and interventional studies. Also, we excluded studies without follow-up. The prespecified primary outcomes was disease recurrence. The secondary outcome was disease related survival.

Selection process

The process of selecting studies involved three distinct stages, wherein the citations identified were independently reviewed for eligibility by two authors (MR and MAO). The initial stage involved assessing the titles obtained from the systematic searches described earlier. Next, we assessed the abstracts of all articles deemed potentially eligible. Full-text articles that met the established criteria were then selected and independently reviewed by both authors for their inclusion in the study. Any discrepancies between the two authors were addressed through discussion or by seeking input from a third author (AB).

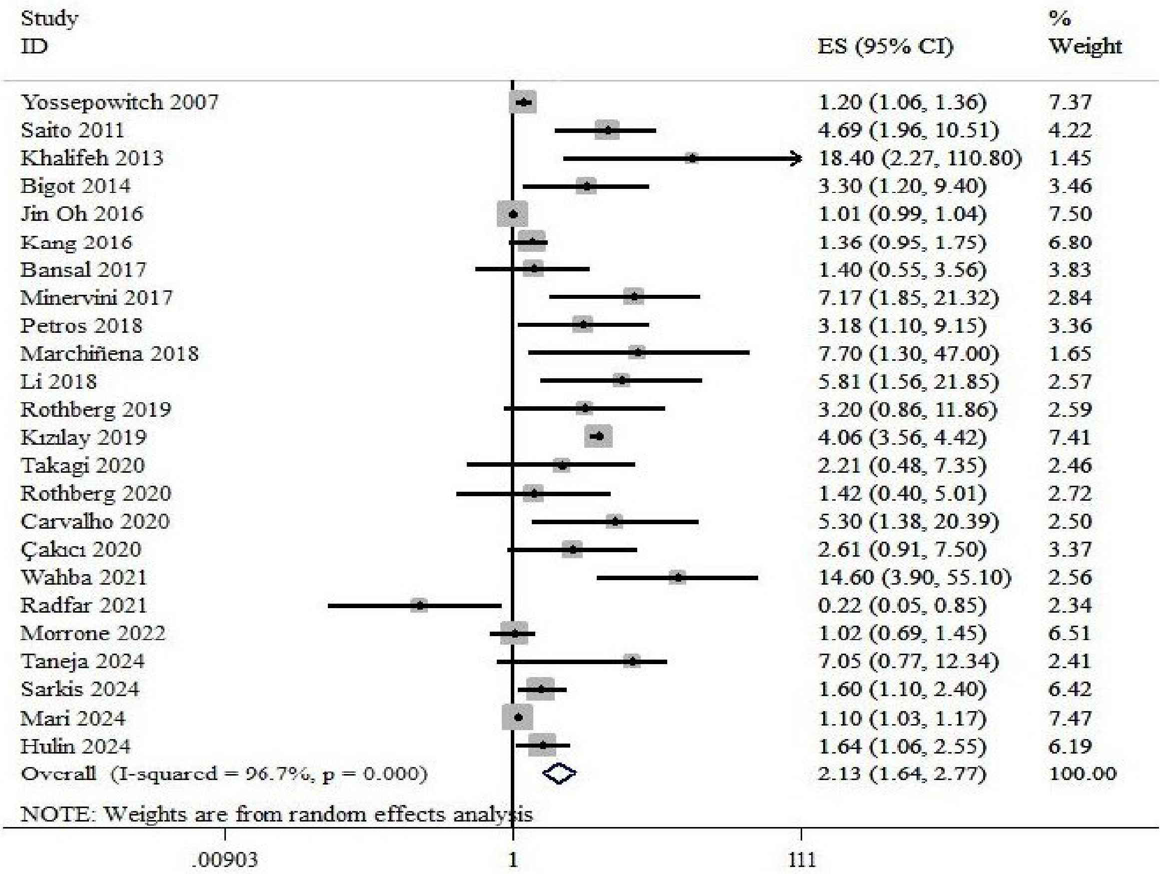

Figure 2. Forest plot detailing risk ratio and 95% confidence intervals for the impact of positive surgical margins on local recurrence.

Data extraction

We included the pre-defined data including the name of first author, year of publication, sample size, tumor size, follow-up, Gender, age, BMI, performance status, surgery duration, ISUP/Fuhrman grade, surgical margin, death, local recurrence, recurrence and effect size for recurrence and survival. The process of extracting data was done independently by two researchers, and if there was a contradiction between the extracted data, it was resolved through consultation, re-examination, or a third person.

Risk of bias assessment

To evaluate the quality of the included studies, we employed the Newcastle-Ottawa Scale (NOS), a widely recognized tool for assessing the risk of bias in non-randomized studies. This step was done independently by two researchers. This scale focuses on three key domains: selection of study groups, comparability of groups, and outcome assessment.

1. Selection: We assessed how well the studies defined their participant groups, ensuring that selection was based on clearly specified criteria. Studies were evaluated on their ability to demonstrate a representative sample and appropriate selection of controls.
2. Comparability: This domain examined the comparability of the study groups regarding relevant factors such as demographic characteristics and baseline health status. We noted any adjustments made for potential confounding variables, enhancing the validity of the findings.
3. Outcome Assessment: We evaluated the methods used for outcome measurement, ensuring that the outcomes were clearly defined and reliably assessed. Studies that utilized validated instruments or standard clinical definitions were rated more favorably.

Each study was rated according to these criteria, receiving a score that reflects its methodological quality. This systematic assessment allowed us to identify potential biases and assess the overall reliability of the evidence presented in the included studies. Any discrepancies in scoring were resolved through discussion among the authors to ensure a consensus was reached.

Data synthesis and analysis

The statistical analysis of this study was done through Stata software version 14. The effect sizes extracted from the studies were in the form of Risk Ratio (RR) and/or Hazard ratio (HR) with 95% confidence intervals according to the type of variables for categorical outcomes. To assess heterogeneity among studies, a random effects model was employed. Both the Q statistic and I2 index were computed to quantify the extent of variability in effect sizes. Studies with I2 values greater than 50% were deemed to exhibit significant heterogeneity. To accommodate this variability and produce more conservative results, a random effects model was utilized. In instances of substantial heterogeneity, subgroup analyses were performed to identify potential sources of variation. Funnel plots were visual-

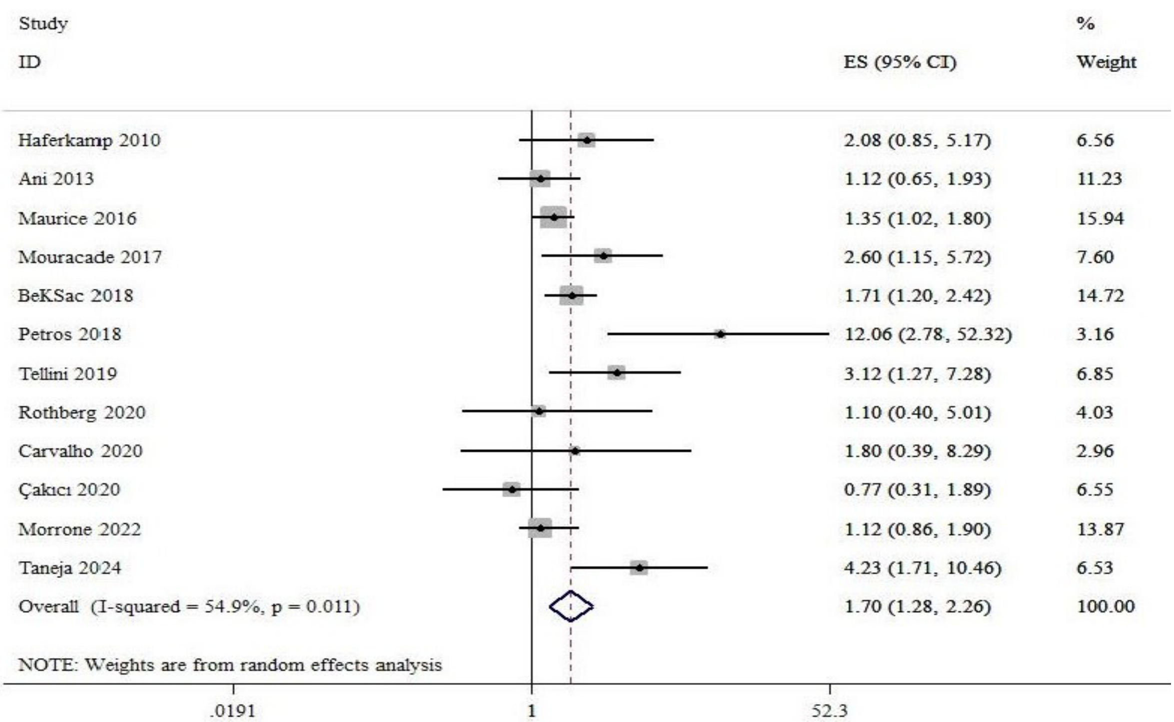

Figure 3. Funnel plots detailing publication bias in the studies evaluated the impact of positive surgical margins on local recurrence

ly inspected to identify potential publication bias. To quantitatively assess asymmetry, Egger's regression test and Begg's test were performed. A trim-and-fill method was applied to estimate the potential impact of missing studies. Sensitivity analysis was conducted using a fixed-effects model, excluding each prospective cohort study individually to evaluate its influence on the overall effect.

RESULTS

Study characteristics

At the end of the systematic search process in official and unofficial databases, 4576 records were obtained; after removing duplicate records, 3245 records entered the first phase of screening. After the first stages of screening, 85 articles entered the second stage of screening, and after reviewing the full text of the articles, 30 original articles were included in this meta-analysis[12, 17-45]. **Figure 1** shows a summary of the article selection process. The baseline characteristics of primary studies were summarized in **Table 1**. Of the 30 included studies, 9 eligible studies (30%) were conducted in USA, 4 in France, 3 in Turkey, 3 in Italy, 2 in Canada, 2 in Japan, 2 in Korea, and one each in Iran, Portugal, Argentina, China and Germany. The 30 studies were published between 2007 and 2024.

Study population

In most of the studies, the examined patients underwent different surgical techniques (open, laparoscopy, and robotic) for small renal masses (around 3 cm of diameter). The pooled data from the included studies revealed a total of 1,797 cases with positive surgical margins and 29,283 cases with negative surgical margins. In the included studies, the number of patients with Positive Surgical Margins varied from 7(8%) to 302(5%). The most frequent histological subtype was clear cell carcinoma and the age range of the patients in most of the studies was between 50 to 65 years old.

Quality of studies

The results of the quality assessment of the included studies are summarized in Table 2. In term of quality assessment based on the Newcastle-Ottawa Quality Assessment Scale, except for four studies that had moderate quality (total score between 4 to 6), most of the studies had high quality (a score equal to or greater than seven).

Association between Positive Surgical Margins and Local Recurrence

In the present study, all of the included studies were reported the association between positive surgical margins and risk of local recurrence. The results of pooled analysis revealed that positive surgical margins significantly increase the risk of local recurrence (RR = 2.13 [95% CI: 1.64, 2.77], P =0.02), with a significant heterogeneity among the evaluated studies ($I^2 = 96.7\%$, $P < 0.001$) (**Figure 2**). In the subgroup analysis, none of the variables (studies quality scores, surgery techniques, follow up duration and sample size) couldn't find the source of heterogeneity. The leave-one-out sensitivity analysis showed that leaving each of the studies had no significant effect on the pooled effect size. Based on the visual inspection of funnel plot, we found an asymmetry (**Figure 3**); however, when we did the Begg (P = 0.52) and Egger's regression tests (P = 0.18), no significant publication bias was seen.

Association between Positive Surgical Margins and Recurrence/Progression-free Survival

In 12 of the included studies, researchers evaluated the effects of positive surgical margins on recurrence/progression-free survival and the results of pooled effect showed that positive surgical margins significantly increase risk of recurrence/progression-free survival (HR=1.70[95% CI: 1.28, 2.26], $P = 0.01$), with a moderate heterogeneity between studies ($I^2 = 54.9\%$, $P = 0.011$) (**Figure 4**). In the subgroup analysis, none of the variables (studies quality scores, surgery techniques, follow up duration and sample size) couldn't find the source of heterogeneity. The leave-one-out sensitivity analysis showed that leaving each of the studies had no significant effect on the pooled effect size. Based on the visual inspection of funnel plot, we found an asymmetry (**Figure 5**); however, when we did the Begg ($P = 0.83$) and Egger's regression tests ($P = 0.47$), no significant publication bias was seen.

DISCUSSION

This systematic review and meta-analysis provide a comprehensive assessment of the impact of PSM following partial nephrectomy on local recurrence and progression-free survival in renal cell carcinoma. Our results indicate that PSM are associated with a 2.13-fold increased risk of local recurrence and a 1.7-fold increase in recurrence/progression-free survival risk, underscoring the prognostic implications of margin status in RCC. This association suggests that positive surgical margins is a potentially independent predictor of adverse oncological outcomes, reinforcing the importance of achieving negative margins in nephron-sparing surgery.

While positive surgical margins can range from 0 to 18% irrespective of the PN technique employed, certain factors have been identified as potential risk contributors. These include tumor dimensions, adipose tissue infiltration, operative blood loss, tumor differentiation, tumor progression stage, RENAL score, and C-index value[35]. Additionally, factors such as tumor grade (ISUP), tumor stage (TNM), the presence of necrosis and capsular invasion, high tumor complexity, and tumor size may influence the likelihood of recurrence and metastasis. These factors may also confound the relationship between positive surgical margins and these outcomes(46).

In our study, PSM were associated with a significantly higher risk of local recurrence and a lower recurrence/progression-free survival. These findings align with one of the previous meta-analysis that showed PSM can increase risk of local recurrence (RR 4.14 95%CI 2.75-6.24)(47). The results of another meta-analysis study that examined the prevalence of PSM after simple enucleation (SE) and standard partial nephrectomy (SPN) for malignant renal tumors showed a prevalence rate of 2.7% (95% CI: 1.5-4.6%) in the SPN method and 0.4% (95% CI: 0.1-2.2%) in SE(48).

This discrepancy may be attributed to differences in study populations, such as tumor characteristics and surgical techniques employed. For instance, our analysis included studies with a wide range of tumor complexities and follow-up durations, which may have amplified the observed heterogeneity. Additionally, variations in definitions of PSM—microscopic vs. macroscopic—and differences in follow-up protocols could account for the discrepancies in recurrence rates and survival outcomes. It is also plausible that advancements in surgical techniques, such as robotic assistance, have contributed to improved margin control and outcomes in more recent studies(48).

The correlation between PSM and recurrence risk may be partly attributed to the residual presence of microscopic cancer cells at the tumor margin(49). Tumor biology likely plays a significant role in determining how PSM affects recurrence and survival. RCC tumors with PSM may exhibit characteristics of aggressive tumor biology, such as a higher grade, larger size, or invasive capabilities, which increase the likelihood of recurrence(16). Also, PSM may leave behind clusters of residual cancer cells that retain their proliferative potential(50). This microenvironment can foster conditions for local recurrence due to the persistence of cancer stem cells or the presence of growth factors and inflammatory signals that promote tumor cell proliferation(51). In the other hand, RCC is a highly vascular tumor, often characterized by dysregulated angiogenesis driven by mutations in the VHL gene. Positive margins may indicate a tumor with high angiogenic potential, which facilitates the formation of new blood vessels and supports tumor growth. Concurrently, RCC has immune-evasive properties, such as PD-L1 expression, which may enable residual tumor cells to escape immune surveillance, leading to recurrence and, potentially, metastasis(52,53).

Recent studies have highlighted the role of Epithelial-Mesenchymal Transition (EMT) in RCC progression. In cases with PSM, residual cells may undergo EMT, a process whereby epithelial tumor cells acquire mesenchymal characteristics, enhancing their motility and invasiveness. This transition not only facilitates local spread but also increases the risk of distant metastases, complicating treatment and diminishing survival outcomes(54,55).

Given the results of our study, the most appropriate course of action for patients with positive surgical margins remains a subject of ongoing debate. Urologists face a challenging decision when confronted with such cases, as both interventional strategies and active surveillance with rigorous follow-up are potential options(56). The optimal approach requires careful consideration of the associated risks of recurrence and the individual patient's clinical characteristics. The available literature indicates that residual tumor tissue is present in 0 to 11% of individuals who undergo radical nephrectomy after a positive surgical margin(57,58). Furthermore, re-resection procedures have been shown to result in residual tumor in approximately 9% of cases. Considering these figures, radical nephrectomy and re-resection may be deemed excessive interventions for patients with positive surgical margins. In such instances, active surveillance may represent a more appropriate management strategy(59).

These mechanisms suggest that PSM may not be merely a surgical outcome but could serve as a marker for aggressive tumor behavior. Therefore, PSM might reflect an underlying biological propensity toward recurrence, making it critical to incorporate this factor into treatment planning and risk stratification(60).

Despite these findings, the study is limited by the significant heterogeneity across included studies, which may stem from variations in surgical techniques (open, laparoscopic, robotic), tumor characteristics (size, grade, histology), and definitions of PSM. For instance, studies may differ in the interpretation of microscopic versus macroscopic margin involvement, impacting the generalizability of findings. Furthermore, the lack of standardized follow-up intervals and imaging protocols may introduce variability in recurrence detection rates. Our subgroup analyses did not identify a definitive source of heterogeneity, suggesting that multifactorial influences contribute to variability in PSM outcomes. Differences in surgical expertise, tumor anatomical location, and underlying patient factors, such as comorbidities, may also play significant roles. Future studies should strive for standardized definitions and consistent follow-up practices to facilitate comparability.

Future research should focus on elucidating the molecular characteristics of RCC tumors that are prone to PSM and subsequent recurrence. Biomarkers predictive of recurrence in the presence of PSM could enhance patient selection for adjuvant treatments, thus enabling a more tailored therapeutic approach. Additionally, clinical trials exploring the efficacy of perioperative and adjuvant therapies specifically in patients with PSM could provide valuable insights into strategies to reduce recurrence risk. Advancements in surgical technology, such as real-time molecular imaging and robotic-assisted surgery, hold promise for enhancing the precision of tumor resection. Research should also investigate the potential of combining intraoperative technologies, like indocyanine green fluorescence imaging, with artificial intelligence-guided margin detection to achieve optimal surgical outcomes.

CONCLUSIONS

Our meta-analysis underscores the significant impact of positive surgical margins on recurrence and progression-free survival following partial nephrectomy for RCC. These findings highlight the need for meticulous surgical planning and margin management in PN to minimize recurrence risks. By advancing the understanding of the biological mechanisms and clinical implications of PSM, this study contributes valuable insights to the field of RCC management, advocating for refined surgical practices, personalized postoperative care, and targeted surveillance strategies. Further research into the development of adjuvant therapies and enhanced surgical techniques will be instrumental in improving outcomes for RCC patients undergoing nephron-sparing surgery.

APPENDIX

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